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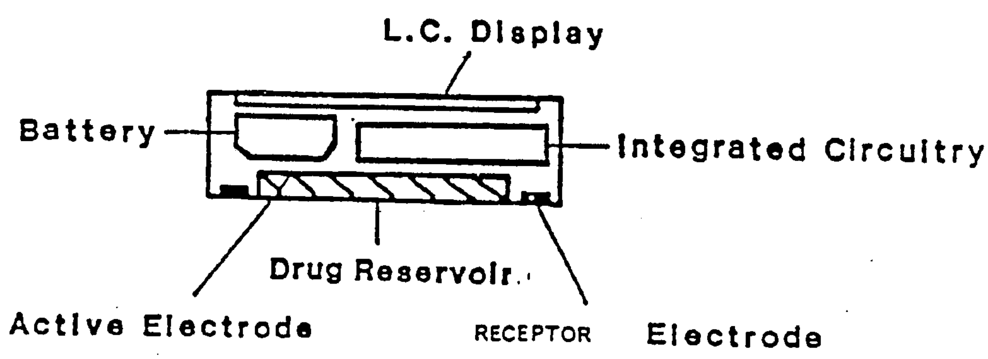
TRANSDERMAL PERIODIC IONTO-THERAPEUTIC SYSTEM

(TPIS)



(57) Abstract

This invention relates to a portable, lightweight iontotherapeutic device for regulated transdermal systemic administration of ionizable pharmaceutical compounds. The device has a preprogrammable control element which controls the iontotherapeutic administration in accordance with a prescription and other instructions entered into the control element by interface with a computer system and which can communicate data on the iontotherapy by interface with a computer system. It also provides an iontotherapeutic process for automated transdermal administration of ionized pharmaceuticals by use of the device. Also provided is a novel battery belt adaptable for use with the device.

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IONTOTHERAPEUTIC DEVICE AND PROCESS

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of U.S. Application Serial No. 07/587,406 filed September 25, 1990 and of U.S. Application Serial No. 07/046,984, filed May 5, 1987, now U.S. Patent No. 5,042,975, which was a continuation-in-part of U.S. Application Serial No. 890,702 filed July 25, 1986, now abandoned.

TECHNICAL FIELD

This invention relates to development of an iontotherapeutic device for regulated transdermal systemic administration of ionizable pharmaceuticals (including ionizable biopharmaceuticals) and a novel battery device usable as an element of said device.

It also provides an iontotherapeutic process for transdermal administration of ionizable pharmaceuticals, particularly those which are otherwise transdermally absorbed to a small degree or not at all. The invention also relates to a polymeric unit dose in which an ionized pharmaceutical is dispersed. The unit dose is adapted to be assembled as a part of either the anode or the cathode, depending upon whether the ionized pharmaceutical is cationic or anionic, so that the ionized pharmaceutical will be delivered transdermally and then be absorbed systemically when the iontotherapeutic device is in operation.

BACKGROUND ART

Many pharmaceuticals are required to be administered to patients by injection. A notable example is insulin, which cannot be administered orally to be effective in lowering the elevated blood sugar levels, which are too high in diabetics (i.e., > 126 mg/dL). Other pharmaceuticals may be administered orally, but in some cases, there is inefficient absorption into the bloodstream to permit the pharmaceuticals to achieve their intended therapy. Also, with regard to oral administration, many orally administered pharmaceuticals undergo a high degree of destruction by the hepatogastrointestinal first-pass metabolism. Often the metabolites of the first-pass metabolism cause unwanted biological activity or toxicity. In oral administration, there are variables which cause undesirable variations in the extent of gastrointestinal absorption from subject to subject, especially in the case of some pharmaceuticals; and there are also associated problems of uneven blood levels resulting from an initial large absorption with attendant undesirable side effects or toxicities, and subsequent blood levels which are less than therapeutically optimal.

Recently there has been an increasing interest in transdermal delivery. However, it is desired that transdermal absorption of a number of pharmaceuticals, particularly the macromolecular drugs such as insulin and cationic drugs like propranolol HCl, be improved.

The hazard and discomfort of administration of pharmaceuticals by injection, especially if therapy is required on a frequent basis, such as the subcutaneous injection of insulin for diabetes therapy, which is required daily, are universally known. There has long been a desire to avoid the necessity of therapy by injection.

Investigations have been carried out to explore the possibility of delivering certain therapeutic agents topically by use of a direct current (DC) iontophoresis. For example, it has been found that fluoride ions can be assimilated into the structure of a tooth with the aid of DC iontophoresis. Also, localized "seating" has been caused by delivering to the skin a sweat-inducing compound, such as pilocarpine, using a direct current. The induced sweat is then assayed using an electrode to determine its chloride ion concentration for diagnosis purposes. A low chloride content in the sweat indicates that a patient may be suffering from cystic fibrosis. Application of a DC iontophoresis can be uncomfortable particularly when the level of applied current is at a high level, in the case of certain pharmaceuticals, in order to achieve a systemic therapeutic level.

It is highly desired to provide improved iontotherapeutic devices and processes and unit dose forms for use therein and to provide further thereby therapeutic levels of systemically-effective pharmaceuticals efficiently with a physiologically-acceptable low electric current.

SUMMARY OF THE INVENTION

A process has been found for administering transdermally a systemically effective amount of an ionizable pharmaceutical in sterile aqueous solution using an iontotherapeutic device such as provided by this invention. The ionized pharmaceutical solution can be contained in a unit dose form such as disposable polymeric matrix unit dose form in which a dosage amount of an ionized pharmaceutical solution (pH desirably at least about 1.0, 1.5 or about 2 pH units above or below the pKa or isoelectric pH of the ionizable pharmaceutical) is intermixed with a polymer which is characterized by being compatible with the pharmaceutical as well as the skin, hydrophilic, and capable of releasing the pharmaceutical for iontotherapeutic transdermal absorption. The unit dose form can also comprise a sterile solution of the ionized pharmaceutical contained within a closed reservoir unit dose form having a drug-releasing microporous membrane surface. The unit dose forms are assembled with a pharmaceutical reservoir electrode and are further adapted to permit the dissolved, ionized pharmaceutical to be delivered iontophoretically to the skin of the subject treated and to provide iontotherapeutic transdermal absorption of a systemically effective amount of the pharmaceutical. The unit dose forms are maintained covered to retain sterility until the desired time of iontotherapeutic administration. A pharmaceutical reservoir electrode which will receive such a unit dose form is used as a part of the

iontotherapeutic device, such as provided by this invention, which is used to carry out the iontotherapeutic delivery and transdermal absorption of the ionized pharmaceutical. The pharmaceutical reservoir electrode is either a cathode or an anode depending upon whether the pharmaceutical is in anionic or cationic form, respectively. The iontotherapeutic device provides, in the process, an iontotherapeutically effective and physiologically acceptable pulse current with a specific waveform having an amplitude such as up to about 10mA based on a reservoir electrode skin-contacting area of about 5 cm^2 and an effective frequency of at least about 10 Hz up to about 50 KHz until the subject treated has received a pharmacologically-effective systemic dosage of the ionized pharmaceutical.

The pharmaceutical administered by this invention can be selected from pharmaceuticals which ordinarily are not transdermally absorbed through intact skin in an effective dosage amount, such pharmaceuticals including but not limited to insulins, vasopressin, heparin, growth hormones, glucagon, oxytocin, and other macromolecular drugs as well as a number of others which can be provided in ionized form. A number of compounds which are naturally-occurring in humans, or variants thereof, and which often are peptide in nature, are also included within this pharmaceutical group, many of which can be produced identically or as a related

compound using DNA recombinant or other biological techniques.

Also provided by the invention is a novel iontotherapeutic device capable of transdermally administering a systemically effective amount of an ionized pharmaceutical. The device is a lightweight, portable transdermal periodic iontotherapeutic device for transdermal administration of a systemically-effective amount of an ionized pharmaceutical, which is adapted to be worn by a subject being iontotherapeutically treated, comprising

1) a DC power supply capable of providing an iontotherapeutically effective and physiologically acceptable DC current in the range up to about 10mA;

2) a periodic waveform generator electrically connected to the DC power supply and having integrated circuitry capable of providing a) a periodic waveform in the square, triangular, sinusoidal, trapezoidal, or other acceptable geometric form or combination thereof; b) an on/off ratio of 1/50 to 10/1; and c) a repetition frequency from about 10 Hz to about 50 KHz;

3) an output circuit electrically connected to said waveform generator which a) can provide a periodic DC current in a pre-selected waveform of said forms; b) monitors current intensity delivered; c) adjusts and maintains the current intensity within predetermined maximum and minimum levels and d) delivers the current to a

reservoir electrode for iontotherapeutic transdermal administration of said ionized pharmaceutical;

4) a pharmaceutical reservoir electrode which can be preselected to be either the cathode or the anode depending upon whether the ionized pharmaceutical is anionic or cationic; said electrode having a receptacle adapted to receive a unit dose of said ionized pharmaceutical in which said ionized pharmaceutical is in aqueous solution at a pH at least 1.0 pH unit below or above the isoelectric point or pKa point of said ionized pharmaceutical ; said electrode with said received unit dose adapted to be placed in electrical contact with the intact skin to be treated iontotherapeutically; said electrode having a terminal to receive and to transmit through said unit dose the said periodic DC current and said unit dose adapted to be in electrical contact with said terminal;

5) receptor electrode adapted to be in electrical contact with the intact skin to be treated and forming with said pharmaceutical reservoir electrode a combination of anode and cathode electrodes;

said electrodes electrically connected to said output circuit and providing when placed upon the skin of a subject being treated a current path through the intervening tissue of the subject being treated; and

6) a preprogramable control element electrically integrated within said device to preprogram and to control said iontotherapeutic administration on an automated basis as in accordance with a physician's prescription entered into the control element, without interaction of a subject being treated with the device for said administration except to permit said subject to stop operation of the device as in the event of an emergency.

The device will ordinarily have a terminal by which the transdermal administration carried on by the device can be monitored using a computer system and a connecting line to connect the device and the computer system or by which a prescription for administration of a pharmaceutical by the device can be entered into the programmable control element by use of a computer system and a connecting line to connect the control element with the computer system.

Further, the device desirably has one or more additional terminals by which the control element can be connected by a connecting line with a sensor to sense a skin condition or with a separate sensor to sense a level of an entity in the body (which correlates with a need for administration of the pharmaceutical), the sensor(s) held in intimate contact with the subject's body and signals said control element on need for administration or skin condi-

tion. For example, in insulin iontotherapy, the signal can transmit the nature of need for insulin administration.

Further, the invention provides a process for administering an ionized pharmaceutical by use of the above defined device and carrying out the following steps:

1) entering a prescription or other instructions into the control element of said device using a computer system;

2) assembling a dosage unit containing a pharmaceutically acceptable aqueous solution of said peptide into a receptacle of a reservoir electrode of a transdermal periodic iontotherapeutic system, which electrode is a cathode or anode depending upon whether such ionized peptide is anionic or cationic, said solution having a pH at least about 1.0 pH unit below or above the isoelectric point of said peptide;

3) placing the cathode and anode electrodes of said transdermal periodic iontotherapeutic system in electrical contact with the intact skin to be treated; and

4) applying an iontotherapeutically effective, periodic DC current of up to about 10mA based on a reservoir electrode/skin-contacting area of about 5 cm^2 using a) a periodic waveform in the square, triangular, sinusoidal, trapezoidal, or other acceptable geometric form, or combinations thereof, b) a physiologically acceptable repetition frequency of at least about 10

Hz, and c) an on/off ratio of from 1/50 to 10/1; said process providing a systemically effective absorption of said peptide pharmaceutical from said solution at a rate of at least 500 percent from that provided by passive diffusion transdermal absorption from said solution during an administration time of at least 2 hours.

The above defined process desirably is carried out wherein a sensor is held in intimate contact with the body of subject being treated such as in intimate contact with the skin of the person being treated and said sensor transmits one or more signals to the control element of the device such as a physiological factor of the subject being treated which correlates with the pharmaceutical administration carried out by the device or a skin condition which relates to the transdermal administration.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a diagram portraying a device of the invention in operation to effect iontotherapeutic transdermal absorption of an ionized pharmaceutical and its uptake into the bloodstream of the subject treated.

FIG. 2 is a block diagram of a transdermal periodic iontotherapeutic device parent application Serial No. 07/046,984.

FIG. 3 is a block diagram of a transdermal periodic iontotherapeutic device coming within the invention.

FIG. 4 is a detailed circuit diagram for the Square-Wave Generator shown in FIGS. 2 and 3.

FIG. 5 is a detailed circuit diagram for the Trapezoidal-Triangular Wave Generator shown in FIGS. 2 and 3.

FIG. 6 is a detailed circuit diagram for the Sinusoidal Signal Generator shown in FIGS. 2 and 3.

FIG. 7 is a detailed circuit diagram for the Output Circuit shown in FIGS. 2 and 3.

FIG. 8 is a block diagram of a wristwatch-type miniaturized periodic iontotherapeutic device coming within the invention, in which the drug reservoir electrode is positioned away from the main portion of iontotherapeutic device.

FIG. 9A and 9B are diagrams illustrating a wristwatch-type miniaturized transdermal periodic iontotherapeutic system with the drug reservoir electrode positioned directly in the lower portion of the iontotherapeutic device and with multifunctional programmability.

FIG. 10 is a block diagram of a portable transdermal periodic iontotherapeutic device.

FIG. 11 and 11A are detailed circuit diagrams of the device shown in FIG. 10.

FIG. 12 is a detailed circuit diagram showing an electronic timer element which can be used to control the iontotherapeutic administration.

FIG. 13 is a schematic diagram of a wrist-type iontotherapeutic device coming within the invention showing a belt-type battery power supply and a sensor for blood sugar monitoring.

FIG. 14 is a schematic diagram showing an iontotherapeutic device of this invention in interface with a computer system through a connecting line (e.g., interface cable/ telephone line).

FIG. 15 is a schematic diagram of an iontotherapeutic device of this invention using a belt or band to attach to the subject being treated.

FIG. 16 is a graph comparing the effects of periodic wave mode and DC mode on the transdermal absorption of insulin and on the reduction of blood glucose level (B.G.L.) in the diabetic hairless rats.

FIG. 17 is a graph showing the time course for the reduction in the blood glucose level (B.G.L.) in the diabetic hairless rates as the result of transdermal delivery of insulin from a pharmaceutical reservoir electrode containing 250 IU of insulin at pH 3.6 by transdermal periodic iontotherapeutic system with square waveform mode (1mA; on/off = 1/1; frequency = 2 KHz) for 40 min.

FIG. 18 is a graph showing the effect of the frequency generated by the transdermal periodic iontotherapeutic system on the reduction in the blood glucose level (B.G.L.) in the diabetic hairless rates using insulin.

FIG. 19 is a graph showing the effect of the on/off ratio in the transdermal periodic iontotherapeutic system on the reduction in the blood sugar level (B.G.L.) in the diabetic hairless rats using insulin.

FIG. 20 is a graph showing the effect of the treatment duration by the transdermal periodic iontotherapeutic system with drug reservoir electrode at pH 3.6, on the reduction in the blood glucose level (B.G.L.) in the diabetic hairless rats using insulin.

FIG. 21 is a graph showing the effect of the treatment duration by the transdermal periodic iontotherapeutic system, with drug reservoir electrode at pH 7.1, on the reduction in the blood glucose level (B.G.L.) in the diabetic hairless rats using insulin.

FIG. 22 is a graph showing permeation of vasopressin facilitated by the transdermal periodic iontotherapeutic system compared to passive diffusion of a vasopressin solution at pH 5.0 through hairless rat skin.

FIG. 23A is a graph showing permeation rate of insulin solution at pH 7.1 through hairless rat skin using no iontotherapy as compared to permeation rate shown in FIG. 21B when using iontotherapy (TIDD).

FIG. 24 is a series of graphs showing the comparative effects of the change in waveform in lowering blood glucose level (B.G.L.) in diabetic hairless rats using transdermal periodic iontotherapeutic system using insulin solution at pH 3.68.

FIG. 25A is a graph showing lowering of blood sugar level (B.G.L.) of hairless rats using transdermal periodic iontotherapeutic system on Day 1 using insulin solution at pH 3.68.

FIG. 25B is a graph showing further lowering of the blood sugar levels of the same rats on Day 3 using transdermal periodic iontotherapeutic system without further administration of insulin, indicating that the insulin delivered transdermally on Day 1 is stored in the skin tissues and can be activated to become available for absorption into systemic circulation on Day 3 by TPIS.

FIG. 26A is a pair of comparative graphs showing plasma immunoreactive insulin levels in diabetic rabbits after administration of insulin solution (pH 7.1) using transdermal periodic iontotherapeutic system (TPIS) compared with corresponding levels in diabetic rabbits using subcutaneous administration (SC). "SZ injection" indicates injections to render rabbits diabetic.

FIG. 26B is a pair of comparative graphs corresponding to those of FIG. 24A showing the respective reduction of blood glucose levels (B.G.L.). The data show that blood glucose levels can be controlled at a highly constant level so as not to fall substantially, if at all, below normal levels by TPIS.

FIG. 27A is a pair of comparative graphs showing the increase in plasma insulin concentration after administration of insulin solution (pH 7.10) using transdermal periodic iontotherapeutic system (TPIS) compared to using transdermal iontotherapeutic system (TIDD) in which 4X current intensity and 2X administration times are used. TPIS administration shows more rapid attainment of increased plasma insulin concentrations.

FIG. 27B is a pair of comparative graphs corresponding to those of FIG. 25A showing the attained lowering of blood glucose levels (B.G.L.). The data show a near instantaneous reduction of blood glucose level from the hyperglycemic level in the diabetic controls using transdermal periodic iontotherapeutic system (TPIS) whereas the reduction using transdermal iontotherapeutic system (TIDD) is lower than the normoglycemic level.

FIG. 28 is a pair of comparative graphs showing a desired reduction in urine output as indicated by urine osmolarity measurement in anesthetized rabbits using transdermal periodic iontotherapeutic system to administer vasopressin solution (pH 5.0). The corresponding graph shows that TPIS is more effective in reducing urine output than TIDD.

FIG. 29 is a graph showing vasopressin permeation rate enhancement when the ionic strength of the vasopressin solution used in TPIS is decreased.

FIG. 30 is a graph showing enhancement of skin permeation of vasopressin using TPIS with a short skin permeation lag time. The graph also shows reversibility of skin permeation within 2 hours after ceasing TPIS treatment and again enhancement of skin permeation after reinstituting TPIS.

DETAILED DESCRIPTION OF THE INVENTION AND THE PREFERRED EMBODIMENTS

FIG. 1 is a diagram portraying a device of the invention in operation to deliver iontotherapeutically an ionized pharmaceutical and its uptake into the bloodstream of the subject being treated. The figure shows the iontotherapeutic device in electrical contact with the skin.

It also shows the pharmaceutical reservoir electrode in contact with the skin as well as the other electrode, which is referred to as the receptor electrode. The electrodes are in contact with the uppermost skin barrier, called stratum corneum. The pharmaceutical is transmitted through the stratum corneum and flows into the dermo-epidermal layer. The stratum corneum is the principal absorption rate limiting barrier. The first portion of the dermis layer is referred to as the papillary layer, which contains a capillary network of the vascular system. The capillary network takes up the transdermally absorbed pharmaceutical and the uptaken pharmaceutical is shown to flow from the capillary network into the main portion of the vascular system.

FIG. 2 is a block diagram of a transdermal periodic iontotherapeutic device coming within the invention in which the power supply is derived either from the conversion of the alternate current (AC) from a 120 V-mains (or other available AC mains) into direct current or from a suitable battery. The power is turned on manually by a switch or automatically by a programmable timer. The device also consists of one or a combination of several electronic multifunction generators, a drug reservoir electrode and a receptor electrode. The multifunction generator is assembled with a power supply, to delivery direct current with periodic waveform of either square, triangular, trapezoidal or sinusoidal shape, to an output circuit. The desired iontotherapeutically-effective waveform can be selected manually or preprogrammed through a switch (K_1), and the frequency of the output waveform can be adjusted in the range of 10 Hz - 50 KHz. The output circuit then provides a physiologically acceptable current, for example, ranging up to 10 mA, to the pharmaceutical reservoir electrode which contains the ionized pharmaceutical to be delivered transdermally, and a receptor electrode in series. When desired, the device can be operated to deliver either DC current alone (periodically or continuously), or in combination with a periodic waveform.

FIG. 3 is a block diagram of an iontotherapeutic device of this invention. It consists of the following elements: a microprocessor, a multiple waveform generator, a waveform selector, an output circuit, a sensor signal processor, a display unit, a power supply with indicator, a reservoir electrode, and a receptor electrode.

The microprocessor is the center of the device. It has the following functions:

a. receiving and processing the physiological signal(s) from the sensor element;
b. communicating with a computer system via an interface cable;
c. receiving and exercising commands from the computer system;
d. storing data and transmitting data to the computer system;
e. controlling operation parameters of the multiple waveform generator, such as frequency and duty cycle of generated waveforms;
f. selecting the input waveform of the output circuit;
g. controlling the operation parameters of the output circuit, such as output current amplitude and treatment cycle;
h. monitoring the load impedance of the device and alerting the user of improper operation conditions.

The microprocessor is made using a commercial single chip microcontroller with necessary expanded memory capacity, additional input/output ports and signal converters. A preferred microcontroller is 80C552 single chip microcontroller made by Signetics, a subsidiary of Philips Components. This microcontroller is very powerful and meets the requirements of the current application. It has the following important features: 16 MHz speed, 8K ROm and 256K RAM memory, 4 watchdog timer-counters, 6 I/O ports and 8 channel 12 bit A/D, UART and I^2C interfaces, and 6 external interrupts.

The multiple waveform generator provides pulse-mode signals of desired waveforms. It can be realized by using the circuitry shown in FIG. 6. It can also be made by using a commercial integrated circuit ICL8038 made by Motorola Corporation.

The waveform selector can be made using a commercial electronic analog switch, such as AD7510 made by Analog Devices.

The output circuit can be made by using the circuit design shown in FIG. 7 or using a three-pin constant current regulator LM334 made by National Semiconductor Corporation.

The function of the sensor signal processor is to further condition the physiological signals, such as blood glucose level signals. It provides necessary function, such as amplification and filtering of the signals. The conditioned signals will be sent to the analog/digital converter

of the microprocessor. They will be used for close-loop control of iontotherapeutic treatment.

The power supply unit consists of battery elements connected in series. The batteries can be either regular ones or rechargeable ones. A low-batter indicator will be used to signal the low battery condition.

FIG. 4 is a detailed circuit diagram for the square wave generator shown in FIG. 2. It employs a microchip 555 timer. The frequency (F) of the square wave is:

$$F = \frac{1}{t_1 + t_2} \qquad t_1 = 0.693\ (P_1 + P_2)\ C$$
$$t_2 = 0.693\ P_1\ C$$

where P's are potentiometers, C is a capacitor, and D's are diodes. During the operation, the capacitor C is charged through the potentiometer P_1 and P_2 and the diode D for t_1 seconds and discharged through potentiometer P_1 and diode D_2 for t_2 seconds. Other circuits can be used in place thereof.

FIG. 5 is a detailed circuit diagram for the triagular-trapezoidal waveform generator shown in FIG. 2. It consists of an integrator (A) and a regenerative comparator (B) connected in a positive feedback loop. Precise triangular waves are formed by integration of the square wave which is fed back from the output of the comparator to the input of the integrator. The frequency (F) of the triangular wave is:

$$F = \frac{1}{t_1 + t_2} \qquad \frac{t^1 = Vo+ - Vo^-)\ R^1}{R_2} \quad \frac{Vo+}{C\ (P_2a + P_3b)}$$

$$\frac{t^1 = Vo+ - Vo^-)\ R^1}{R_2} \quad \frac{{}^-Vo^-}{C\ (P_2a + P_3b)}$$

where Vo+ and Vo^- are the higher and lower trip points of the comparator, respectively. Resistors R_1 and R_2 control the comparator trip points. Capacitor C is the integration capacitor. Potentiometer P_1 provides adjustment of the triangular wave offset. Potentiometers P_2 and P_3 adjust frequency and symmetry, respectively.

The third op-amp circuit (C) acts as a damper. It produces a trapezoidal wave with the same frequency as the triangular wave. Potentiometer P_4 sets the clamping level. Other circuits can be used in place thereof.

FIG. 6 is a detailed circuit diagram for the sinusoidal signal generator shown in FIG. 2. The circuit of the generator uses two amplifiers: one (A) acts as a non-inverting integrator, and other (B) acts as an inverting integrator. They are connected in cascade to form a feed-back loop. The frequency (F) of the sinusoidal signal is determined by:

$$F = \frac{1}{2\ CP}$$

C's and P's are integration capacitors and the variable resistors, respectively. Resistor R_1 is a feedback resistor. Capacitor C_1 is used to prevent high-frequency oscillations. Other circuits can be used in place thereof.

FIG. 7 is a detailed circuit diagram for the Output Circuit shown in FIG. 2. The desired waveform is selected manually or automatically from the 3 generators through a switch (K_1) and sent to the inverting amplifier, from which the signal then goes to the output stage of two transistors. The output current (dose current0 is adjusted by a potentiometer (P), as monitored by a current meter (A), and is delivered to the drug reservoir electrode (B). Other circuits can be used in place thereof.

FIG. 8 is a diagram illustrating the wristwatch-type miniaturized transdermal periodic iontotherapeutic system with multifunction programmability. It is designed to have one or more nuclear batteries and two pieces of microchips: one for the purpose of generating different waveforms, as outlined in FIGS. 4-6, and the other is for the purpose of controlling and to display the output current. The nuclear batteries provide the energy needed for long-term operation. For instance, the programmability may include selection of DC alone or in combination with a periodic waveform, a dose current for a particularly designated time period. In certain applications, it may be advantageous in operating the devices of this invention to have the periodic current wave-

form remaining at some constant DC level during the off cycle. In this design of iontotherapeutic device, the drug reservoir electrode is positioned outside the device.

FIG. 9 shows an embodiment of another design of iontotherapeutic device. It shows two views of the device. The first view is a cross-sectional view showing the integrated circuitry, L.C. display, battery, drug reservoir electrode positioned directly in the lower central portion of the base and the receptor electrode encircling the drug reservoir electrode. The next view shows the bottom view of the device. In the center portion of the bottom view is shown the circular drug reservoir portion of the drug reservoir electrode. The drug or pharmaceutical dissolved in an aqueous solution is homogeneously dispersed in a polymer matrix unit dose as described herein. The pharmaceutical solution can also be contained in a reservoir-type unit dose having a microporous surface adapted to permit the drug to be transmitted. Next, there is shown the receptor electrode, as a circular ring positioned in spaced relationship from the drug reservoir electrode. At the top of the cross-sectional view is shown a liquid crystal display. It can display a number of functions, including whether or not the device is in operation, the type of periodic current and waveform being used and other pertinent information of the transdermal periodic iontotherapeutic drug delivery. The battery employed as the power source for this invention can

be a lithium or other nuclear battery having a voltage, for example, of from 6 to 12 volts.

FIG. 10 is a block diagram of a portable transdermal periodic iontotherapeutic device in which the power supply is derived from a battery source such as one or more 9V batteries. The power is turned on manually by a switch. The device can be equipped so that it can be turned on automatically by a programmable timer. The device also consists of one or a combination of several electronic multifunction generators, a drug reservoir electrode and a receptor electrode. The multifunction generator can provide periodic waveform of either square, triangular, trapezoidal or sinusoidal shape, to an output circuit. The desired iontotherapeutically effective waveform can be selected manually and the frequency of the output waveform can be adjusted to a physiologically acceptable frequency of at least 10 Hz and up to about 50 KHz. The output circuit then provides a physiologically acceptable current, ranging up to 10 mA, to the pharmaceutical reservoir electrode, which contains the solution of the ionized pharmaceutical to be delivered transdermally, and a receptor electrode in series. When desired, the device can be operated to deliver either DC current alone (periodically or continuously), or in combination with a periodic waveform.

FIGS. 11 and 11A show a detailed circuit diagram for the portable transdermal periodic iontotherapeutic device shown in the block diagram of FIG. 10. Referring to FIG.

11, the following is a description of the circuits and their functioning:

The DC-to-DC converter and battery voltage monitor

$1C_1$, R_1-R_4, C_1-C_3, L1 and diode IN914 consist of a DC-to-DC converter which is incorporated in step-up application. The output voltage is elevated from 9V battery to 27V with the proper adjustment of R_4. The output voltage of the battery is monitored by a battery voltage monitor which includes a zener diode D_1, R_5-R_7, C_4 and C106Y1. When output of 9-V battery drops below minimum acceptable volume of 8.3V, LED lights to indicate the need for recharging.

Pulse generator and constant current output stage

IC_2, D_2-D_5, T_1, C_5, C_6 and R_8 are components of a triangle-wave generator. In this circuit, the charge and discharge currents for C_6 come through the diode bridge formed by D_2-D_5. Bridge D_2-D_5 consists of four general purpose switching diodes with low-leakage characteristics, that serve to steer current in the proper direction through the current source made up of T_1 and R_8.

The pin 3 of IC_2 serves as a source of current for the timing network, and its state of high or low determines the direction of current flow into or out of C_6 for charge or discharge. Since both charge and discharge currents flow through the same current regulator circuit, the currents are

equal, and thus times of charge and discharge are equal. As a result, triangular waves are formed across C_6.

The circuit covers the frequency range of about 20 Hz to 30 KHz. The adjustment of the frequency is done with R_8. The frequency of the triangle waves can be expressed as

$$f = \frac{i}{5R_8C_6}$$

The output of the triangle-wave generator is sent to the pin 3 of IC_3 which serves as a comparator. The voltage comparison is made between pin 1 and pin 3 of IC_3. The square waves are formed at pin 7 of IC_3 with a duty cycle which is determined by the voltage of the voltage divider composed of R_{10}-R_{12}. The higher the voltage applied to pin 2 is, the shorter the "on" time of the square waves, and vice versa. The duty cycle of the square waves covers the range of 1/10 to 10/1. The square waves are amplified by T_2-T_4 and sent to pin 11 of IC_4.

In constant current output stage, IC_{923} is employed to serve as a current regulator. IC_{923} is originally designed to be a voltage regulator with an output current limit resistor R across pin 10 and pin 3. The maximum output current is set as 0.6/R. This feature is adapted to form a current regulator. As soon as the condition $(V_{out}/R_L)>I_s$ is satisfied (where V_{out} is the output voltage, R_L, load resistance, and I_s, output current preset), the output current will be kept at the preset level.

R_{21} is the minimum current limit resistor. R_{22} is used to preset the desired output current. C_7 and R_{20} are used to eliminate high frequency noise.

Output current monitor

Intersil 7106 interfaced with a liquid crystal display is the heart of the current monitor. R_{23} is a shunt resistor. C_8 and R_{24} consist of an RC oscillator which runs at about 48 KHz and is divided by four prior to being used as the system clock. C_{10} and R_{27} serve as an input filter. C_{11}, C_{12} and R_{28} determine the display sensitivity. C_9 is for auto-zero function.

The power is turned on manually by a switch or automatically by a programmable timer. The device also consists of one or a combination of several electronic multifunction generators, a drug reservoir electrode and a receptor electrode. The multifunction generator is assembled with a power supply, to deliver direct current with periodic waveform of either square, triangular, trapezoidal or sinusoidal shape, to an output circuit. The desired iontotherapeutically effective waveform can be selected manually or programmed through a switch (K_1), and the frequency of the output waveform can be adjusted in the range of 10 Hz - 50 KHz. The output circuit then provides a physiologically acceptable current, ranging up to 10 mA, to the pharmaceutical reservoir electrode, which contains the pharmaceutical formulation to be delivered transdermally, and a receptor

electrode in series. When desired, the device can be operated to deliver either DC current alone (periodically or continuously), or in combination with a periodic waveform.

FIG. 12 is a detailed circuit diagram for the timer of the multi-channel transdermal periodic iontotherapeutic device shown in the block diagram of FIG. 12. Referring to FIG. 12, the following is a description of the circuit, and their functioning:

Timer

The timer consists of ten IC chips, two relays and other components, IC_8 provides a system clock. IC_1, IC_3 an IC_5 are quad 2-input multiplexers which consist of four 2-input multiplexers with common select and enable inputs. When the select input is at logical "o", the four output pins assume the values of inputs of pin 1, 5, 14, 11, otherwise, inputs of pin 3, 6, 13, 10. The inputs of the first group represent the "off" time of the timer which has a maximum value of 999 minutes. The inputs of the second group represent the "on" time of the timer which has a maximum value of 99 minutes. The values of both "on" and "off" time needed are set through BCD thumbwheels.

IC_2, IC_4 and IC_6 are "decade-down" counters which receive preset values from multiplexers. The pin 15's of these counters will become logical "o" when the minimum count is reached. When all three counters reach the minimum, IC_9, a "AND" gate, will turn to be logical "1". This

pulse is inverted by IC_{10} and goes to reset the system clock, reloads counters and converts IC_7, which consists of two Flip-Flop's. At the instant when "on" time is finished, the pin 3 and pin 5 turn to be logical "o", which opens two relays and turns on the red LED> AT the same time, the pin 2 and pin 6 turns to be logical "1", which will load the values representing the "on" time to pin 4, 7, 9, 12 of three multiplexers and turns off the green LED. At the instant when "off" time is finished, the pin 3 and pin 5 turn to be logical "1", which will load the values representing the "off" time to pin 4, 7, 9, 12 of three multiplexers and turns on the green LED. The whole cycle of both "on" and "off" is repeated for any desired length of time. The switch K_2 is used to interrupt the operation and trigger the timer.

Pulse generator and constant current output stages

IC_{13}, diode bridge consisting of four IN_{914}, T_1, R_{28} and C_5-C_7 are components of a triangle wave generator. In this circuit, the charge and discharge currents for one of C_6-C_{17} come through the diode bridge formed by four IN_{914}, which serve to steer current in the proper direction through the current source made up of T_1 and R_{28}.

The pin 3 of IC_2 serves as a source of current for the timing network, and its state of high or low determines the direction of current flow into or out of the capacitor for charge or discharge. Since both charge and discharge cur-

rents flow through the same current regulator circuit, the currents are equal and thus times of charge and discharge are equal. As a result, triangular waves are formed across the working capacitor C.

The circuit covers the frequency range of about 10 Hz to 30 KHz. The adjustment of the frequency is done by the selection of the proper capacitor through a multi-stop switch. The frequency of the triangle waves can be expressed as

$$f \cong \frac{1}{5R_{28}C}$$

The output of the triangle wave generator is sent to the pin 3 of IC_{14} which serves as a comparator. The voltage comparison is made between pin 2 and pin 3 of IC_{14}. The square waves are formed at pin 7 of IC_{14} with a duty cycle which is determined by a voltage-divider composed of R_{322}-R_{34}. The higher the voltage applied to pin 2 is, the shorter the "on" time of the square waves, and vice versa. The duty cycle of the square waves covers the range of 1/10 to 10/1. The square waves are amplified by T_2 and T_3 and then sent to three voltage followers T_4-T_6.

At the "on" time of the timer, two relays are closed and emitters of T_4-T_6 are connected to pin 11's of IC_{15}-IC_{17}. IC_{15}-IC_{17} provide three-channel current outputs. Three IC_{923} are employed to serve as current regulators. IC_{923} is originally designed to be a voltage regulator with an output current limit resistor R across pin 10 and pin 3.

The maximum current is set as 0.6/R. This feature is adapted to form a current regulator. As soon as the condition $(V_{out}/R_L)>I_s$ is satisfied (where V_{out} is the output voltage, R_L load resistance and I_s output voltage, R_L load resistance and I_s output current preset), the output current will be kept at the present level. R_{40}, R_{45} and R_{50} are maximum current limit resistance respectively. R_{41}, R_{46} and R_{51} are used to preset the desired current. C_{19}-C_{21} are used to eliminate high frequency noise.

The output currents are monitored by a current meter A. The switch K_1 is used to select DC or pulse output. Other circuits can be used in place thereof.

FIG. 13 is a schematic diagram of a device of this invention. It shows a wristwatch-type device which houses the iontotherapeutic device in the center in connection with a belt-type battery package. The display unit, emergency on/off switch, the input/output port, the interface cable to a computer system, and the sensor input port are also shown. This device can be comfortably worn by a patient during the treatment. The weight of such device of this invention will ordinarily be 5 oz. or less, preferably 3 oz. or less.

FIG. 14 is a schematic diagram of a wrist-type iontotherapeutic device of this invention showing a connection with a computer patient data and control system such as at a clinical site or at a physician's office. The communication between the iontotherapeutic device and a computer system

serves two purposes. It allows the commands and data according to the physician's prescription to transfer to the iontotherapeutic device via an interface cable. It also allows the physician to read and assess the important data of treatment using the device. By using telephone lines, the communication can be to a remote site.

Various computers are satisfactory for use in the computer system, including personal computers and larger computers. Various suitable programs can be used in the communication.

FIG. 15 is the schematic diagram of an iontotherapeutic device of this invention using a belt or band to attach to the subject being treated. Inside the belt there are battery elements connected in series. These batteries can be either regular ones or rechargeable ones. The battery belt can also be made into a shape of jewelry. The battery belt can be designed to house different numbers of battery elements to power different treatment periods. The belt can be made of suitable material such as plastic or leather materials or metals or combinations of materials. Its length can be adjusted as needed.

FIG. 16 is a graph showing the time course for the reduction of the elevated blood glucose level (% change in B.G.L.) in the diabetic hairless rats as the result of transdermal delivery of insulin from the drug reservoir electrode (containing 250 IU of insulin at pH 7.1) by Transdermal Periodic Iontotherapeutic System for 80 minutes and

the effect of current delivery mode. Keys: (0) direct current made (2 mA), ( ) Square wave periodic mode (2 mA; on/off = 4/1; Frequency = 2000 Hz).

FIG. 17 is a graph showing the time course for the reduction of the elevated blood glucose level (% change in B.G.L.) in the diabetic hairless rats as the result of transdermal delivery of insulin from the pharmaceutical reservoir electrode (containing 250 IU of insulin at pH 3.6) by Transdermal Periodic Iontotherapeutic System with square wave periodic mode (1 mA; on/off = 1/1; Frequency = 2000 Hz) for 40 minutes.

FIG. 18 is a graph showing the effect of the frequency generated by the Transdermal Periodic Iontotherapeutic System on the reduction of the elevated blood glucose level (% change in B.G.L.) in the diabetic hairless rats. The frequency of 2000 Hz produces a greater magnitude and a longer duration of reduction than the 1000 Hz.

FIG. 19 is a graph showing the effect of the on/off ratio in the Transdermal Periodic Iontotherapeutic System on the reduction of the elevated blood glucose level (% change in B.G.L.) in the diabetic hairless rats. By regulating the ratio, the magnitude and the duration of reduction in B.G.L. in the diabetes can be controlled as desired.

FIG. 20 is a graph showing the effect of the treatment duration by the Transdermal Periodic Iontotherapeutic System on the reduction of the elevated blood glucose level (%

change in B.G.L.) in the diabetic hairless rats. At pH 3.6, which is lower than the isoelectric point of insulin (pH 5.3), with the dose current of 1 mA, on/off ratio of 8/1 and at a frequency of 2000 Hz, the treatment duration of 20-40 minutes appears to be equally effective.

FIG. 21 is a graph showing the effect of the treatment duration by the Transdermal Periodic Iontotherapeutic System on the reduction of the elevated blood glucose level (% change in B.G.L.) in the diabetic hairless rats. AT pH 7.1, which is higher than the isoelectric point of insulin (pH 5.3), with the dose current of 1 mA, on/off ratio of 1/1 and at frequency of 1000 Hz, the treatment duration produces a difference in the rate and the duration, but with equal effectiveness.

For a more detailed description of the background for the remaining FIGS., see the indicated Examples: FIG. 22 (Example 11); FIGS. 23A and 23B (Example 12); FIG. 24 (Example 14); FIG. 25 (Example 15); FIGS. 26A and 26B (Example 16); FIG. 27 (Example 17); FIG. 28 (Example 18); FIG. 29 (Example 19); FIG. 30 (Example 20).

In carrying out the iontotherapeutic process for administering transdermally, systemically measured amounts of an ionized pharmaceutical compound, it is first necessary to provide the pharmaceutical-containing unit dose in which the pharmaceutical is in aqueous solution. The pH of the aqueous solution is adjusted to an effective Ph either below or above the pKa or the isoelectric point of the pharmaceu-

tical. It is desirable to adjust the pH to an effective level of about 1 pH unit above or below the pKa or isoelectric point of the pharmaceutical, preferably to an effective pH level of at least 1.5 or at least 2 pH units below or above the pKa or isoelectric point of the pharmaceutical. With particular pharmaceuticals, it is preferable to so adjust the pH either below or above the pKa or isoelectric point. For example, with regard to insulins, it is preferable to adjust the pH below the pKa or isoelectric point, such as to about 1.0 pH units or lower below, which for commercial insulins is about pH 5.3.

The formed unit dose is placed in the receptacle portion provided in the pharmaceutical reservoir electrode, so that the ionized pharmaceutical can be transdermally absorbed. If the unit dose form is a preformed self-contained unit dose, it can be held in the receptacle portion of the reservoir electrode by customary means such as clamping, snapping into position, adhesive, or the like.

One convenient form of the unit dose for the ionized pharmaceutical solution is to disperse uniformly the aqueous solution of the ionized pharmaceutical in a polymeric matrix. The polymeric unit dose must be characterized by being able to release the ionized pharmaceutical, when the iontotherapeutic device is in operation, so that the ionized pharmaceutical can be absorbed transdermally. The unit dose

is in electrical contact with the skin of the subject being treated when the iontotherapeutic device is in operation.

For a description on making suitable unit dose in the form of a polymeric matrix dosage unit, reference is made to parent U.S. Application Serial No. 07/046,984, filed May 5, 1987, now U.S. Patent Application No. 5,042,975, which is incorporated herein by reference.

Additionally, descriptions are found in parent U.S. Application Ser. No. 07/587,406, filed September 25, 1990, which is incorporated herein by reference.

The pharmaceuticals suitable for delivery by this polymer disc can be the anti-diabetic drugs, such as insulins or sulfonyl ureas; the anti-diuretic peptide drugs, such as vasopressin; the calcium-channel blocker-type anti-hypertensive drugs, such as verapamil; the beta-blocker type anti-hypertensive drugs, such as propranolol; narcotic analgesic drugs, such as hydrocodone; non-steroidal anti-arthritic drugs, such as indomethacin; anti-bacterial antibiotics, such as tetracyclines, penicillins and cephalosporins; anti-neoplastic drugs, such as methotrexate; and the peptide hormones, such as luteinizing hormone-releasing hormone (LHRH), oxytoxin, and the like.

Pharmaceuticals suitable for use in the process of this invention can be selected from the following or other ionizable pharmaceuticals which are capable of being transdermally absorbed in the iontotherapeutic process, the following systemically-effective pharmaceuticals expected to be

capable of delivery by an iontotherapeutic device as developed in this invention: Propranolol HCl, Ibuprofen, Indomethacin HCl, Lorazepaml, Thioridazine Hcl, Tolazamide, Doxycycline, Flurazepam, Minocycline, Disopyramide, Metocloprimide HCl, Cephalothin sodium, Thiothixene, Vincristine, Oxazepam, VAlproic acid, Temazepam, Hydralizine HCl, Ampicillin sodium, Amantadine HCl, Acetohexamide, Haloperidol, Doxepin, Cyclobenzaprine HCl, Sucralfate, Cephalaxin, Cefazolin sodium, Ampicillin, Cefadroxil, Hydralizine HCl, Reserpine and Hydrochlorthiazide, Clindamycin HCl, Carbenicillin disodium, Piroxicam, Fenoprofen calcium, Dialtiazem HCl, Chlorpropamide, Sulindac, Nefedipine, Cimetidine, Naproxen, Piroxicam, Ranitidine HCl, Nadolal, Alprozolam, Captopril, Triazolam, Chlordiazepoxide, Amitryptilline, Dobutamide, Sulfamethoxazole, Trimethoprin, and the like.

The ionizable peptide pharmaceuticals used in the processes and the unit doses of this invention and administered by the devices of this invention are those which are pharmaceutically effective and transdermally absorbable. Desirably the peptides have at least five amino acid units and more desirably at least nine amino acid units.

In operating the process, using for example a wrist-watch-type iontotherapeutic device such as provided by this invention, the appropriate unit dose containing the pharmaceutical required for the desired therapy is assembled in the receptacle portion of the pharmaceutical reservoir elec-

trode. For example, if insulin is to be administered and the pH of the insulin solution in the dose unit is pH 3.6, insulin is a cationic and therefore the dosage unit is assembled as a part of pharmaceutical reservoir electrode, which is the anode. The desired waveform is selected and preprogrammed, such as a square waveform. The pharmaceutical reservoir electrode used preferably is adapted to receive a disposable unit dose, e.g., a polymeric matrix unit dose, and to make electric contact with the skin of the subject being treated. Such means is assembled in place. The other variables are selected and preprogrammed, such as the frequency, the dose current and on/off ratio. The device is attached to the subject being treated as by a band attached to the device and adapted to be attached to and detached from the subject. The switch of the device is turned to "on" position and the device commences operation of the iontotherapeutic process, which causes the ionized pharmaceutical of reservoir electrode to be administered transdermally and iontotherapeutically to provide a systemic dosing. The particular waveform, mA, pharmaceutical reservoir electrode (i.e., cathode or anode), frequency, length of treatment and other factors will be selected and preprogrammed depending upon the pharmaceutical being administered, the subject being treated and others.

Some pharmaceuticals, especially certain relatively low molecular weight pharmaceuticals, can be iontotherapeutically administered using either periodic DC mode or periodic

wave mode. For example, the periodic DC mode can be "on" for about 0.5 to about 10 minutes, preferably about 1 to about 5 minutes per hour. During the intervening period during the hour, the device is in "off" position. The "on" period can be more frequent or less frequent, if desired, to provide effective treatment, such as one "on" period every 30 minutes or every ninth minute. In Example 5, it is shown that hydrocodone can be administered following this general procedure. The dose currents, the on/off ratios, the dosage units and the devices described above can be used or adapted to be used in the practice of the periodic DC mode process.

A few hours duration of treatment each day following either procedure is ordinarily adequate, for example, 2 to 10 hours, depending upon factors such as the pharmaceutical, the subject being treated, the iontotherapeutic factors selected and the like.

The following Examples are illustrative of the invention but are not intended to be limiting.

Example 1

An aqueous solution of insulin at concentration of 250 IU/ml is prepared by dissolving 96.9 mg (25.8 IU/mg) of pure insulin in 10 ml of double-distilled, sterile water and adjusted to pH 7.1 with 0.5N NaOH. Two ml of the insulin solution so prepared is filled into a refillable dosage unit having a microporous membrane as the drug-releasing surface. This insulin-containing reservoir-type dosage unit is then assembled as a part of the pharmaceutical reservoir electrode and applied on the abdominal skin of 3 diabetic hairless rats with the transdermal periodic iontotherapeutic system operating at 2 mA with direct current mode or square-wave periodic mode (on/off = 4/1; Frequency = 2000 Hz). The results on the reduction in blood glucose level are shown and compared in FIG. 16.

Example 2

An amount of 200 mg (25.8 IU/mg) of pure insulin is dissolved in 10 ml of double-distilled, sterile water and the pH is adjusted to 3.6 with 0.5N HCl. An amount of 200 mg of hydroxypropylmethylcellulose is well dispersed in another 10 ml of double-distilled sterile water using a magnetic stirrer with a stirring bar (5 cm in length) at a rotation speed of 600 rpm. The temperature is controlled at

about 80^{o}C. After the hydroxypropylmethylcellulose is dispersed homogeneously, the stirring is continued while the mixture is cooled to about 40^{o}C.

The insulin solution prepared above is then added to the dispersion of hydroxypropylmethylcellulose with intermittent stirring to avoid any denature of insulin molecules, using the same stirring mechanism as described above, at the same stirring rate of 600 rpm for a period of two minutes. The insulin/hydroxypropylmethylcellulose solution is then placed in a refrigerator for congealing to occur. The insulin-containing polymer matrix is cut into disc-shaped parts with the appropriate dimensions, such as 2.5 cm in diameter and 0.2 cm in thickness. The insulin-containing discs are stored at 5^{o}C. The concentration of insulin in the discs is about 250 IU/gm.

The insulin-containing polymeric matrix dosage forms are removed as needed and assembled into the pharmaceutical reservoir electrode. The pharmaceutical reservoir electrode having the insulin-containing polymer unit dose form is the anode since the insulin molecules in the polymeric matrix dose units are cations at pH 3.6, which is lower than the isoelectric point of insulin (pHiso = 5.3).

Application of this insulin-containing polymeric matrix unit dose is made onto the abdominal skin of 3 diabetic hairless rats. The transdermal periodic iontotherapeutic system is then operated at 1 mA using an on/off ratio of 1/1, a frequency of 2000 Hz and a square wave mode, for 40

minutes. The result on the reduction in blood glucose level is shown in FIG. 17.

Example 3

An aqueous solution of insulin at a concentration of 250 IU/ml is prepared by dissolving 193.8 mg (25.8 IU/mg) of pure porcine insulin in 20 ml of citrate buffer at pH 3.6. Two ml of the insulin solution so prepared is filled into a refillable dosage unit having a microporous membrane as the drug-releasing surface. This insulin-containing reservoir-type dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device and applied successively on the abdominal skin of 9 diabetic hairless rats with the transdermal periodic iontotherapeutic system operating at 1 mA with square waveform mode to study the effect of frequency, on/off ratio and treatment duration on the reduction of blood glucose level. The results are shown and compared, respectively in FIGS. 18, 19 and 20.

Example 4

The same insulin solution is prepared in the same way as in Example 1, except that a phosphate butter at pH 7.1 is used to replace the double-distilled water. Two ml of the insulin solution so prepared is filled into a refillable dosage unit having a microporous membrane as the drug-releasing surface. This unit dose is applied to 3 diabetic hairless rats following the same operation procedures as in

Example 3 to study the effect of treatment duration on the reduction of blood glucose level. The results are shown in FIG. 21.

Example 5

A saturated solution of hydrocodone 9pKa = 8.56), a narcotic analgesic drug, is prepared in citrate buffer at pH 4.0 and in phosphate buffer at pH 7.5. An aliquot of 3.5 ml of this hydrocodone solution is filled into the reservoir compartment, which is in contact with the stratum corneum surface of the hairless rat abdominal skin, of each Valia-Chien skin permeation cell with the receptor compartment containing equal volume of a pH 7.4 buffered isotonic (drug-free) saline solution. The transdermal periodic iontotherapeutic system is then mounted with its electrodes immersing in the skin permeation cell, one electrode in each of the two solution compartments. A current of 1 mA is applied for 2 min. periodically on the hour for 12 hours at either DC mode or periodic square wave mode (frequency, 2000 Hz; on/off ratio, 1/1). The results are shown in Table I.

Table I: Enhancement in Rate and Reduction in Time Lag of the Skin Permeation Rate of Hydrocodone, a Narcotic Analgesic Drug, by the Transdermal Periodic Iontotherapeutic System

	Skin Permeation Rate ($mcg/cm^2/hr \pm S.D.$)		
Mode	pH 7.5	pH 4.0	T_{lag} (hrs)
Control	4.75 ± 1.70	3.10	5.17
DC mode	7.61 ± 2.74	37.5	0.72
periodic wave mode	7.01 ± 1.16	59.4	0.90

Example 6

A saturated solution of methotrexate, an anti-neoplastic drug, is prepared in double-distilled water and adjusted to pH 8.0, which is higher than the pKa values of methotrexate (4.8 and 5.5). An aliquot of 3.5 ml of this methotrexate solution (2 mg/ml) is filled into the donor compartment, which is in contact with the stratum corneum surface of the hairless rat abdominal skin, of each Valia-Chien skin permeation cell with the receptor compartment containing equal volume of a pH 7.4 buffered isotonic (drug-free) saline solution. The transdermal periodic iontotherapeutic system is then mounted with its electrodes immersed in the skin permeation cell, one electrode in each of the two solution compartments. A DC current of 1 mA is applied for 10 minutes periodically on the hour for 5 hours with a frequency of 2000 Hz, a square wave form, and an on/off ratio of 4/1. The results are illustrated in Table II:

Table II: Enhancing Effect of Transdermal Periodic Iontotherapeutic System (TPIS) on the Skin Permeation of Methotrexate - An Anti-Neoplastic Drug

Time	Cumulative Amount of Drug Absorbed (mcg/cm^2)	
(hrs)	No TPIS	With TPIS
1.33	0.0086	0.0820
2.33	0.0247	0.1373
3.33	0.0471	0.4223
4.16	0.0745	0.5705
5.16	0.1398	1.0835

Example 7

A saturated solution of propranolol (pKa = 9.45), a beta-blocker type anti-hypertensive drug, is prepared in citrate buffer at pH 3.68. The enhancing effect of the transdermal periodic iontotherapeutic system is studied under the same conditions as that outlined in Example 6. The results are shown in Table III:

Table III: Enhancing Effect of Transdermal Periodic Iontotherapeutic System (TPIS) on the Skin Permeation of Propranolol (1) - An Anti-Hypertensive Beta-Blocker Drug

Time (hrs)	Cumulative Amount of Drug Absorbed (mcg/cm^2) No TPIS	With TPIS (2)
1.5	0.0691	0.5970
2.5	0.2615	1.1950
3.5	0.5845	3.3650
4.5	0.9955	5.2150
5.5	2.0800	9.0700

1) In the Valia-Chien skin permeation cell, a donor solution containing 13.3 mg/ml of propranolol (pKa = 9.45) at pH 3.68 was applied topically to hairless rat skin at 37°C.

2) TPIS applied a DC current of 1mA periodically at 10 min/hr, a frequency of 2000 Hz and an on/off ratio of 4/1.

Example 8

A saturated solution of verapamil (pKa = 8.9), a calcium-channel blocker-type anti-hypertensive drug, is prepared in citrate buffer at pH 3.68. The enhancing effect of the transdermal periodic iontotherapeutic system is studied under the same conditions as that outlined in Example 6. The results are shown in Table IV.

Table IV: Enhancing Effect of Transdermal Periodic Iontotherapeutic System (TPIS) on the Skin Permeation of Verapamill(1) - A Calcium-Channel Blocker-Type Antihypertensive Drug

Time (hrs)	Cumulative Amount of Drug Absorbed (mcg/cm_2)	
	No TPIS	With TPIS(2)
1.42	<0.0001	0.297
2.42	<0.0001	0.445
3.42	-	0.695
4.17	-	0.973
5.17	<0,0001	1.945

1) In the Valia-Chien skin permeation cell, a donor solution containing 23.95 mg/ml of verapamil (pKa = 8.9) at pH 3.68 is applied topically to hairless rat skin at 37_0C.

2) TPIS applied a DC current of 1 mA periodically at 10 min/hr, a frequency of 2000 Hz and an on/off ratio of 4/1.

Example 9

A saturated solution of tetracycline HCl (pKa = 3.3, 7.8 and 9.7), an antibiotic drug, is prepared in phosphate buffer at pH 9.0. The enhancing effect of the transdermal periodic iontotherapeutic system is investigated under the same conditions as that outlined in Example 6. The results are shown in Table V:

Table V: Enhancing Effect of Transdermal Periodic Iontotherapeutic System (TPIS) on the Skin Permeation of Tetracycline Hcl$_{(1)}$ - A Calcium-Channel Blocker-Type

Time	Cumulative Amount of Drug Absorbed (mcg/cm$_2$)	
(hrs)	No TPIS	With TPIS$_{(2)}$
1.25	0.0180	0.1765
2.25	0.0550	0.2555
3.25	0.0650	0.7815
4.25	0.1450	1.3235
5.25	0.3040	3.5600

1) In the Valia-Chien skin permeation cell, a donor solution containing 6.2 mg/ml of tetracycline HCl (pKa = 3.3, 7.8 and 9.7) at pH 9.0 is applied topically to hairless rat skin at 37$_{0}$C.

2) TPIS applied a DC current of 1 mA periodically at 10 min/hr, a frequency of 2000 Hz, a square waveform and an on/off ratio of 4/1.

Example 10

A saturated solution of indomethacin (pKa = 4.5), a non-steroidal anti-arthritic drug, is prepared in buffer solution at pH 2.5, which is 2 pH units below the pKa, and at pH 5.5, which is one pH unit above the pKa, and at pH 4.5, the pKa. The enhancing effect of the transdermal periodic iontotherapeutic system is evaluated under the same conditions as that outlined in Example 6. The results are shown in Table VI.

Table VI: Enhancing Effect of Transdermal Periodic Iontotherapeutic System (TPIS) on the Skin Permeation of Indomethacin - A Non-Steroidal Anti-Arthritic Drug

TPIS*	Skin Permeation Rate ($mcg/cm_2/hr$)		
	pH 2.5	pH 4.5	pH 5.5
No	-	-	1.47
Yes	0.76	0.44	6.30

*TPIS applied a DC current of 1.2 mA periodically at 5 min/hr, for 7 hours, with a frequency of 2000 Hz, a square waveform and an on/off ratio of 2/1.

Example 11

An aqueous buffer solution of vasopressin (50 mcg/ml containing 1.7 mcCi/ml H_3-vasopressin) is prepared in citrate-phosphate buffer at pH 5.0. An aliquot of 3.5 ml of this vasopressin solution is filled into the refillable dosage unit having a microporous membrane as the drug-releasing surface. The dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device and membrane surface thereof is applied to the stratum corneum side of hairless rat skin mounted in the Valia-Chien skin permeation cell at 37_0C. Samples are withdrawn at regular intervals and radioactivity is measured by scintillation counter to determine the amount of vasopressin which has been transdermally absorbed.

The results demonstrate that vasopressin permeates through the hairless rat skin at constant, but slow rate for 30 hours (0.94 $\pm$ 0.62 ng/cm_2/hr) (FIG. 22).

When the skin is treated with transdermal periodic iontophoretic system (TPIS) at current intensity of 0.5 and 1mA, frequency of 2 KHz, on/off ratio of 1/1, and at the rate of 10 min. per 40 min. for 4 hours, the skin permeation profiles are enhanced with rate increases from 0.94 ($\pm$0.62) ng/cm_2/hr (referred to as "passive diffusion" in FIG. 20) to 116.2 ($\pm$ 10.7) and 178.0 ($\pm$ 25) ng/cm_2/hr, respectively. After the treatment with transdermal periodic iontophoretic system, referred to in following Table VII as "post-activation phase," the rate of skin permeation of vasopressin is reduced to the basal rate of only 0.7 ($\pm$ 0.4) and 5.3 ($\pm$ 0.5) ng/cm_2/hr, respectively. The results of the experiment are shown in FIG. 22 and in the following Table VII.

Table VII: Effect of TPIS on Skin Permeation Rate of Vasopressin

No TPIS	0.0 mA	9.12 (±1.06)	0.94	(±0.62)
With TPIS				
a) Activation phase(2)	0.5 mA	<0.5	116.2	(±0.4)
b) Post-Activation phase	0.0 mA	---	0.7	(±0.4)
a) Activation phase(2)	1.0 mA	<0.5	178.0	(±25.0)
b) Post-Activation phase	0.0 mA	---	5.3	(±0.5)

1) In-vitro permeation across hairless rat skin mounted in the Valia-Chien permeation cell.

2) Application of DC at on/off ratio of 1/1 and frequency of 2 KHz, by multi-channel TPIS unit (shown in FIG. 22 for 10 min. per 40 minute period, treatment repeated for six 40-minute cycles.

Example 12

An aqueous solution of insulin (5.3 IU/ml containing 0.3 mcCi of I_{125}-insulin) is prepared and adjusted to pH 7.1 using naOH. An aliquot of 3.5 ml of this insulin solution is filled into the refillable dosage unit having a micro-porous membrane as the drug-releasing surface. The dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device and membrane surface thereof is applied to the stratum corneum side of hairless rat skin mounted in the Valia-Chien skin permea-

tion cell at 37_{o}C. Samples are withdrawn at regular time intervals and radioactivity is measured by scintillation counter to determine the amount of insulin which has been transdermally absorbed.

The results demonstrate that insulin permeates through the hairless rat skin at constant, but at a slow rate for 48 hours (3.94 $\pm$ 0.29 mcIU/cm_2/hr) (FIG. 23A).

When the skin is treated with transdermal therapeutic system (TIDD) at current intensity of 1mA, frequency of 0 Hz, on/off ratio of 1/1, and at the rate of 5 min. per 60 min. for 7 hours, the skin permeation profiles are enhanced with rate increased from 3.94 ($\pm$0.29) mcIU/cm_2/hr to 37.5 ($\pm$4.5) mcIU/cm_2/hr. FIG. 23B shows comparison of insulin permeation data in FIG. 23A using no iontotherapy (0) over a 7-hr. period with permeation data of same insulin solution using TIDD iontotherapy.

Example 13

An aqueous solution of insulin (5.3 IU/ml containing 0.3 mcCi of I_{125}-insulin) is prepared and adjusted to pH 3.7, 5.2 or 7.1 using either HCl or naOH solution. An aliquot of 3.5 ml of this insulin solution is filled into the refillable dosage unit having a microporous membrane as the drug-releasing surface. The dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device and membrane surface

thereof is applied to the stratum corneum side of hairless rat skin mounted in the Valia-Chien skin permeation cell at 37_oC. Samples are withdrawn at regular time intervals and radioactivity is measured by scintillation counter to determine the amount of insulin which has been transdermally absorbed.

The results demonstrate that insulin permeates through the hairless rat skin at constant, but at a slow rate for 48 hours, with permeability coefficient ranging from 6.50 ($\pm$4.2) to 10.02 ($\pm$1.94)x 10_{-7} cm/hr (Table VIII). Permeabiity coefficient is the ratio of the steady state rate of skin permeation of the pharmaceutical which is transdermally absorbed/the concentration of the pharmaceutical solution which is applied transdermally. The pharmaceutical in this experiment is insulin.

When the skin is treated with transdermal therapeutic system (TIDD) at current intensity of 1mA, frequency of 0 Hz, on/off ratio of 1/1, and at the rate of 5 min. per 60 min. for 7 hours, the skin permeation profiles are enhanced with skin permeability coefficient increased to a range from 70.76 ($\pm$8.56) x 10_{-7} to 242.59 ($\pm$18.43) x 10_{-7} cm/hr, which show dependence on solution pH. The lower pH solution (pH 3.7) shows greater increase in TPIS-facilitated skin permeability.

Table VIII: Skin Permeability Coefficient of Insulin (Hairless Rats)

Donor Solution	Permeability Coefficient (cm/hr± SE) x 10 (1)	
pH	No TIDD	With TIDD
3.7	6.50 (±1.42)	242.59 (±18.43)
5.2	10.02 (±1.94)	120.07 (±22.86)
7.1	7.43 (±0.54)	70.76 (±8.56)

(1) Triplicate Determinations

Example 14

An aqueous buffer solution of insulin (250 IU/ml) is prepared in citrate-phosphate buffer at pH 3.68. An aliquot of 2.5 ml of this insulin solution is filled into the refillable dosage unit having a microporous membrane as the drug-releasing surface. The dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device and membrane surface thereof is applied to the skin at abdominal region of 3 groups of anesthetized, diabetic hairless rats. Blood samples are withdrawn at regular time intervals and glucose levels are measured by glucose analyzer. The reduction in glucose level from hyperglycemic state is the pharmacodynamic response to the insulin absorbed transdermally. The results demonstrate that when the skin is treated with transdermal periodic iontophoretic system (TPIS) at current intensity of 1 mA, frequency of 2 KHz, on/off ratio of 1/1, for 40 min.

the blood glucose levels are reduced substantially. The data show that the time course and the extent of reduction in blood glucose levels in diabetic rats vary with the type of waveform used (FIG. 24).

Example 15

An aqueous buffer solution of insulin (250 IU/ml) is prepared in citrate-phosphate buffer at pH 3.68. An aliquot of 2.5 ml of this insulin solution is filled into the refillable dosage unit having a microporous membrane as the drug-releasing surface. The dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device and membrane surface thereof is applied to the skin at abdominal region of 5 anesthetized, diabetic hairless rats. Blood samples are withdrawn at regular time intervals and glucose levels are measured by glucose analyzer. The reduction in glucose level from hyperglycemic state is the pharmacodynamic response to the insulin absorbed transdermally. The results demonstrate that when the skin is treated on Day 1 with transdermal periodic iontophoretic system (TPIS) with insulin in the pharmaceutical reservoir electrode at current intensity of 1 mA, frequency of 2 KHz, square waveform, on/off ratio of 1/1, for 40 min. the blood glucose levels are reduced substantially (FIG. 25A). On Day 3, the diabetic rats are treated again with TPIS with no insulin in the pharmaceuti-

cal reservoir electrode (placebo formulation), the blood glucose is also reduced, indicating that part of the insulin delivered transdermally on Day 1 forms a depot in the skin tissue and can be triggered to be systemically absorbed on Day 3 (FIG. 25B).

Example 16

An aqueous buffer solution of insulin (500 IU/ml) at pH 7.10 is used. An aliquot of 2.5 ml of this insulin solution is filled into the refillable dosage unit having a micro-porous membrane as the drug-releasing surface. The dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device and membrane surface thereof is applied to the skin at dorsal region of 3 diabetic rabbits. Blood samples are withdrawn at regular time intervals and analyzed for immunoreactive insulin concentration by radioimmunoassay and for glucose levels by glucose analyzer. The reduction in glucose level from hyperglycemic state is the pharmacodynamic response to the insulin absorbed transdermally. The results demonstrate that when the skin is treated with transdermal periodic iontophoretic system (TPIS) at current intensity of 1 mA, frequency of 2 KHz, on/off ratio of 1/1, and square waveform for 40 min. the plasma immunoreactive insulin concentration increases rapidly and the blood glucose levels are reduced substantially. The plasma insulin profile (FIG. 26A) as well as the time course and the extent of reduction in blood

glucose levels (FIG. 26B) in diabetic rabbits are compared with the results from the conventional subcutaneous administration of insulin. The data show that plasma insulin concentrations as well as blood glucose levels can be effectively controlled using TPIS system of this invention. FIG. 24B shows that by using the TPIS system of this invention the blood glucose level (B.G.L.) can be appropriately reduced in a more controlled manner than by daily SC dosages so as to prevent B.G.L. to fall below normal levels.

Example 17

An aqueous buffer solution of insulin (500 IU/ml) at pH 7.10 is used. An aliquot of 2.5 ml of this insulin solution is filled into the refillable dosage unit having a microporous membrane as the drug-releasing surface. The dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device and membrane surface thereof is applied to the skin to the abdominal skin of 2 groups of diabetic rabbits. Blood samples are withdrawn at regular time intervals and analyzed for immunoreactive insulin concentration by radioimmunoassay and for glucose levels by glucose analyzer. The reduction in glucose level from hyperglycemic state is the pharmacodynamic response to the insulin absorbed transdermally. The results demonstrate that when the skin is treated with transdermal periodic iontophoretic system (TPIS) at current

intensity of 1 mA, frequency of 2 KHz, on/off ratio of 1/1, and square waveform for 40 min., the plasma immunoreactive insulin concentration increases more rapidly and the blood glucose levels are reduced more instantaneously than transdermal iontophoretic delivery (TIDD) at current intensity of 4 mA for 80 min. (FIG. 27). The data in FIGS. 25A and B show that the TPIS system of this invention provides both a more rapid increase in plasma insulin concentration after administration and a more rapid reduction in blood glucose level than use of TIDD even though the corresponding current intensity in the TIDD system is 4 times as much (4 mA vs. 1 mA) and administration is 2 times as great (80 minutes vs. 40 minutes) as in the TPIS system.

Example 18

An aqueous buffer solution of vasopressin (40 IU/ml) is prepared in citrate-phosphate buffer at pH 5.0. Vasopressin is an anti-diuretic pharmaceutical, which is used by patients which have an excessive urine output. Vasopressin caused a reduction of urine output and an increase in ion content, such as sodium ion content. Ion content in the urine is determined by using osmolarity measurement. An aliquot of 3.5 ml of this vasopressin solution is filled into the refillable dosage unit having al microporous membrane as the drug-releasing surface. The dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device and membrane sur-

face thereof is applied to the abdominal skin of 2 groups of anesthetized rabbits. Blood samples are withdrawn and urine samples are collected at regular time intervals and urine osmolarity is measured by osmometer. The increases in osmolarity from the basal level are the pharmacodynamic responses to the vasopressin transdermally absorbed.

The results demonstrate that when the skin is treated with transdermal periodic iontophoretic system (TPIS) at current density of 0.22 mA/cm_2, frequency of 2 KHz, on/off ratio of 1/1, and square waveform for 40 min., the urine osmolarity increases from the basal levels more rapidly and substantially than with transdermal iontophoretic delivery (TIDD) under the same experimental conditions (FIG. 28).

Example 19

An aqueous buffer solution of vasopressin (50 mcg/ml containing 1.7 mcCi/ml H_3-vasopressin) is prepared in citrate-phosphate buffer at pH 7.4 with varying ionic strengths. An aliquot of 3.5 ml of this vasopressin solution is filled into the refillable dosage unit having a microporous membrane as the drug-releasing surface. The dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device and membrane surface thereof is applied to the stratum corneum side of hairless rat skin mounted in the Valia-Chien skin permeation cell at 37_oC. Samples are withdrawn at regular

time intervals and radioactivity is measured by scintillation counter to determine the amount of vasopressin which has been transdermally absorbed. The results demonstrate that vasopressin permeates through the hairless rat skin at constant, but slow rate for 30 hours (1.32 $\pm$0.38 $ng/cm_2/hr$). When the skin is treated with transdermal periodic iontophoretic system (TPIS) at current intensity of 1 mA, frequency of 2 KHz, on/off ratio of 1/1, and at the rate of 10 min. per 40 min. for 4 hours, the skin permeation profiles are enhanced with rate increases from 1.32 ($\pm$0.38) $ng/cm_2/hr$ (referred to as "passive diffusion") to the range of 65.9 ($\pm$13.1) to 632 ($\pm$65.0) $ng/cm_2/hr$, depending upon the ionic strength of vasopressin solution. The results of the experiment are shown in the following Table IX.

Table IX: Effect of Ionic Strength on Skin Permeation Rate of Vasopressin

<u>Ionic Strength</u>	<u>Skin Permeation Rate</u>[1] ($ng/cm_2/hr \pm SD$)	<u>Enhancement Factor</u>[2]
0.488	65.9 ($\pm$ 13.1)	49.9 ($\pm$ 18.0)
0.244	101.4 ($\pm$ 9.1)	76.8 ($\pm$ 6.9)
0.122	244.6 ($\pm$ 26.3)	185.3 ($\pm$ 19.9)
0.061	632.6 ($\pm$ 65.0)	472.8 ($\pm$ 59.0)

[1] The rates determined in the activation phase with lag time ranging from 0.48 ($\pm$ 0.21) to 0.86 ($\pm$ 0.15) hrs.

[2] Compared to the skin permeation rate of vasopressin by passive diffusion (1.32 $ng/cm_2/hr$).

The TPIS-facilitated skin permeation rate appears to be dependent upon the ionic strength of drug solution. The lower the ionic strength, the higher the rate of skin permeation and the greater the enhancement in skin permeability (FIG. 29).

Example 20

An aqueous buffered solution of vasopressin (50 mcg/ml containing 1.7 mcCi/ml H_3-vasopressin) is prepared in citrate-phosphate buffer at pH 5.0 at ionic strength of 0.064. An aliquot of 3.5 ml of this vasopressin solution is filled into the refillable dosage unit having a microporous membrane as the drug-releasing surface. The dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device and membrane surface thereof is applied to the stratum corneum side of hairless rat skin mounted in the Valia-Chien skin permeation cell at 37_oC. Samples are withdrawn at regular time intervals and radioactivity is measured by scintillation counter to determine the amount of vasopressin which has been transdermally absorbed.

The results demonstrate that vasopressin permeates through the hairless rat skin at constant, but slow rate for 30 hours (0.98 ± 0.26 $ng/cm_2/hr$).

When the skin is treated with transdermal periodic iontophoretic system (TPIS) at current intensity of 0.3 mA frequency of 16 KHz, on/off ratio of 1/1, for 60 min., the skin permeation profiles are enhanced with rate increases from 0.98 ($\pm$ 0.26) $ng/cm_2/hr$ referred to as "passive diffusion") to 757.3 ($\pm$ 53.2) $ng/cm_2/hr$ (FIG. 28), while the duration of time lag is reduced from 9 hours down to 0.40 ($\pm$ 0.06) hours). The data in FIG. 30 demonstrate the reversibility of skin permeability that in less than 2 hours after the TPIS treatment, the skin permeability returns to the rate before the TPIS treatment. Then, TPIS can be applied again to facilitate the skin permeation of vasopressin.

What is Claimed is:

1. A lightweight, portable transdermal periodic iontotherapeutic device for transdermal administration of a systemically-effective amount of an ionized pharmaceutical, which is adapted to be worn by a subject being iontotherapeutically treated, comprising

1) a DC power supply capable of providing an iontotherapeutically effective and physiologically acceptable DC current in the range up to about 10mA;

2) a periodic waveform generator electrically connected to the DC power supply and having integrated circuitry capable of providing a) a periodic waveform in the square, triangular, sinusoidal, trapezoidal, or other acceptable geometric form or combination thereof; b) an on/off ratio of 1/50 to 10/1; and c) a repetition frequency from about 10 Hz to about 50 KHz;

3) an output circuit electrically connected to said waveform generator which a) can provide a periodic DC current in a pre-selected waveform of said forms; b) monitors current intensity delivered; c) adjusts and maintains the current intensity within predetermined maximum and minimum levels and d) delivers the current to a reservoir electrode for

iontotherapeutic transdermal administration of said peptide pharmaceutical;

4) a pharmaceutical reservoir electrode which can be preselected to be either the cathode or the anode depending upon whether the ionized pharmaceutical is anionic or cationic; said electrode having a receptacle adapted to receive a unit dose of said peptide pharmaceutical in which said peptide is in aqueous solution at a pH at least 1.0 pH unit below or above the isoelectric point of said peptide; said electrode with said received unit dose adapted to be placed in electrical contact with the intact skin to be treated iontotherapeutically; said electrode having a terminal to receive and to transmit through said unit dose the said periodic DC current and said unit dose adapted to be in electrical contact with said terminal;

5) receptor electrode adapted to be in electrical contact with the intact skin to be treated and forming with said pharmaceutical reservoir electrode a combination of anode and cathode electrodes;

said electrodes electrically connected to said output circuit and providing when placed upon the

skin of a subject being treated a current path through the intervening tissue of the subject being treated; and

6) a preprogramable control element electrically integrated within said device to preprogram and to control said iontotherapeutic administration on an automated basis as in accordance with a physician's prescription entered into the control element, without interaction of a subject being treated with said device for the administration except to permit said subject to stop operation of the device as in the event of an emergency.

2. A device of Claim 1 which has electrically connected with the control element thereof a sensor.

3. A device of Claim 2 wherein the sensor senses a level of a physiological entity in the body of the subject which correlates with the pharmaceutical being administered iontothereapeutically and signals said information to said control element.

4. A device of Claim 2 wherein the sensor senses a predetermined skin condition of the body of the subject and signals the information to said control element.

5. A device of Claim 1 wherein the device interfaces with a computer system to enter into the control element thereof a preprogrammed prescription and other instructions or to receive data on the functioning of the device.

6. A device of Claim 1 wherein the device is a wrist-band type.

7. A transdermal periodic iontotherapeutic process for administering a controlled and systemically effective amount of an ionized pharmaceutical which is stable for transdermal administration and is transdermally absorbable using a device as defined in Claim 1, by

1) entering a prescription or other instructions for administering said pharmaceutical into the control element of said device;

2) assembling a dosage unit containing a pharmaceutically acceptable aqueous solution of said ionized pharmaceutical into a receptacle of a reservoir electrode of said device, which electrode is a cathode or anode depending upon whether said ionized peptide is anionic or cationic, said solution having a pH at least about 1.0 pH unit below or above the isoelectric or pKa point of said pharmaceutical;

3) placing the cathode and anode electrodes of said transdermal periodic iontotherapeutic system in electrical contact with the intact skin to be treated;

4) applying upon command of said control element an iontotherapeutically effective, periodic DC current of up to about 10 mA based on a reservoir electrode/skin-contacting area of about 5 cm_2 using a) a periodic waveform in the square, triangular, sinusoidal, trapezoidal, or other acceptable geometric form, or combinations thereof, b) a physiologically acceptable repetition frequency of at least about 10 HZ, and c) an on/off ratio of from 1/50 to 10/1; said process providing a systemically effective absorption of said ionized pharmaceutical from said solution at a rate of at least 500 percent from that provided by passive diffusion transdermal absorption from said solution during an administration time of at least 2 hours.

8. A process of Claim 7 wherein the ionized pharmaceutical is an ionized peptide pharmaceutical.

9. A process of Claim 7 in which the pH of the pharmaceutical solution is at least about 1.5 pH units below or above the isoelectric or pKa point of said pharmaceutical.

10. A process of Claim 7 in which the pH of the pharmaceutical solution is at least about 2.0 pH units below or above the isoelectric or pKa point of said pharmaceutical.

11. A process of Claim 7 in which the pH of the pharmaceutical solution is at least about 1.5 or about 1.0 pH units below the isoelectric or pKa point of said pharmaceutical.

12. A process of Claim 7 in which the ionized pharmaceutical is insulin and the pH of the insulin solution is in the range of about pH 3.0 to pH 4.0.

13. A process of Claim 7 in which the pH of the insulin solution is about pH 3.6.

14. A process of Claim 7 in which the current intensity is not more than about 5 mA based on a reservoir electrode/skin-contacting area of about 5 cm_2.

15. A process of Claim 7 in which the current intensity is not more than about 2 mA based on a reservoir electrode/skin-contacting area of about 5 cm_2.

16. A process of Claim 1 in which the current intensity is not more than 1 mA based on a reservoir electrode skin-contacting area of about 5 cm_2.

17. A process of Claim 7 wherein the solution is an insulin solution having a pH which is at least about 1.5 pH units lower or higher than the isoelectric point of the insulin, the current intensity not more than about 2 mA based on a reservoir electrode skin-contacting surface area of about 5 cm_2, the administration times are not more than about 40 minutes, and the repetition frequency is at least about 1000 Hz.

18. A battery belt adapted to be worn around the wrist or other part of a subject's body to power an electronic device used by said subject, said device comprising
   1) a band adapted to house batteries;
   2) said batteries connected in series;
   3) a terminal electrically connected with the series of batteries adapted to connect electrically through a connecting line with said electronic device.

19. A battery belt of Claim 18 adapted for use with a device of Claim 1.

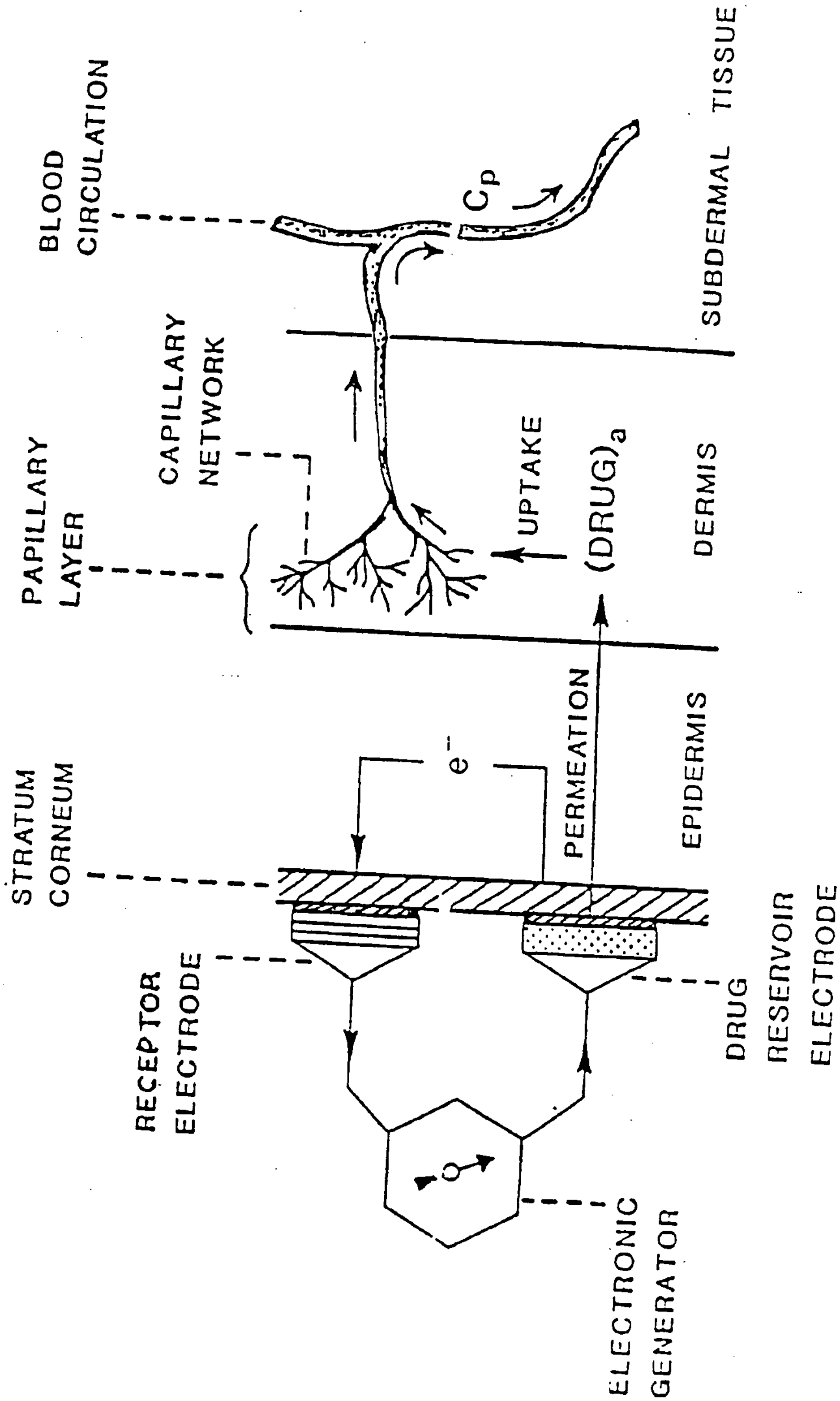

BLOOD CIRCULATION
SUBDERMAL TISSUE
C_p
CAPILLARY NETWORK
PAPILLARY LAYER
UPTAKE
$(DRUG)_a$
DERMIS
STRATUM CORNEUM
e^-
PERMEATION
EPIDERMIS
RECEPTOR ELECTRODE
DRUG RESERVOIR ELECTRODE
ELECTRONIC GENERATOR

FIG. I

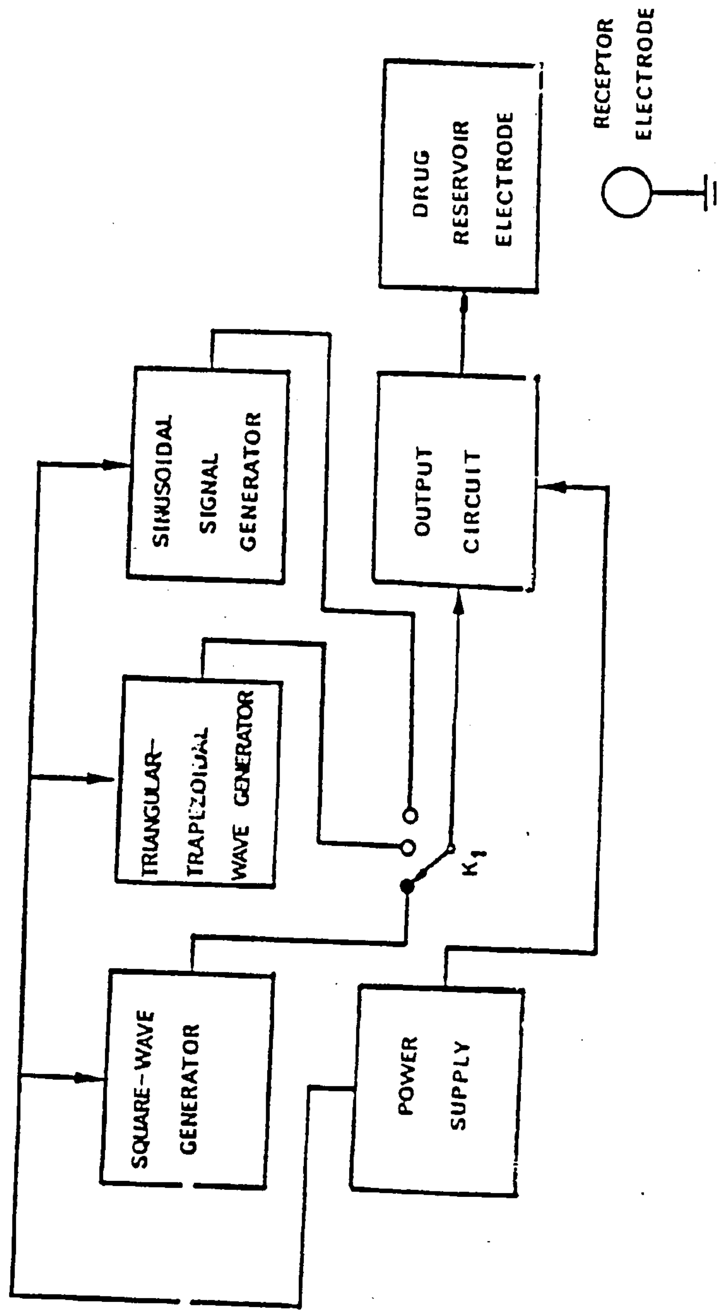

DRUG
RESERVOIR
ELECTRODE
RECEPTOR
ELECTRODE
SINUSOIDAL
SIGNAL
GENERATOR
OUTPUT
CIRCUIT
TRIANGULAR-
TRAPEZOIDAL
WAVE GENERATOR
K1
SQUARE-WAVE
GENERATOR
POWER
SUPPLY

FIG. 2

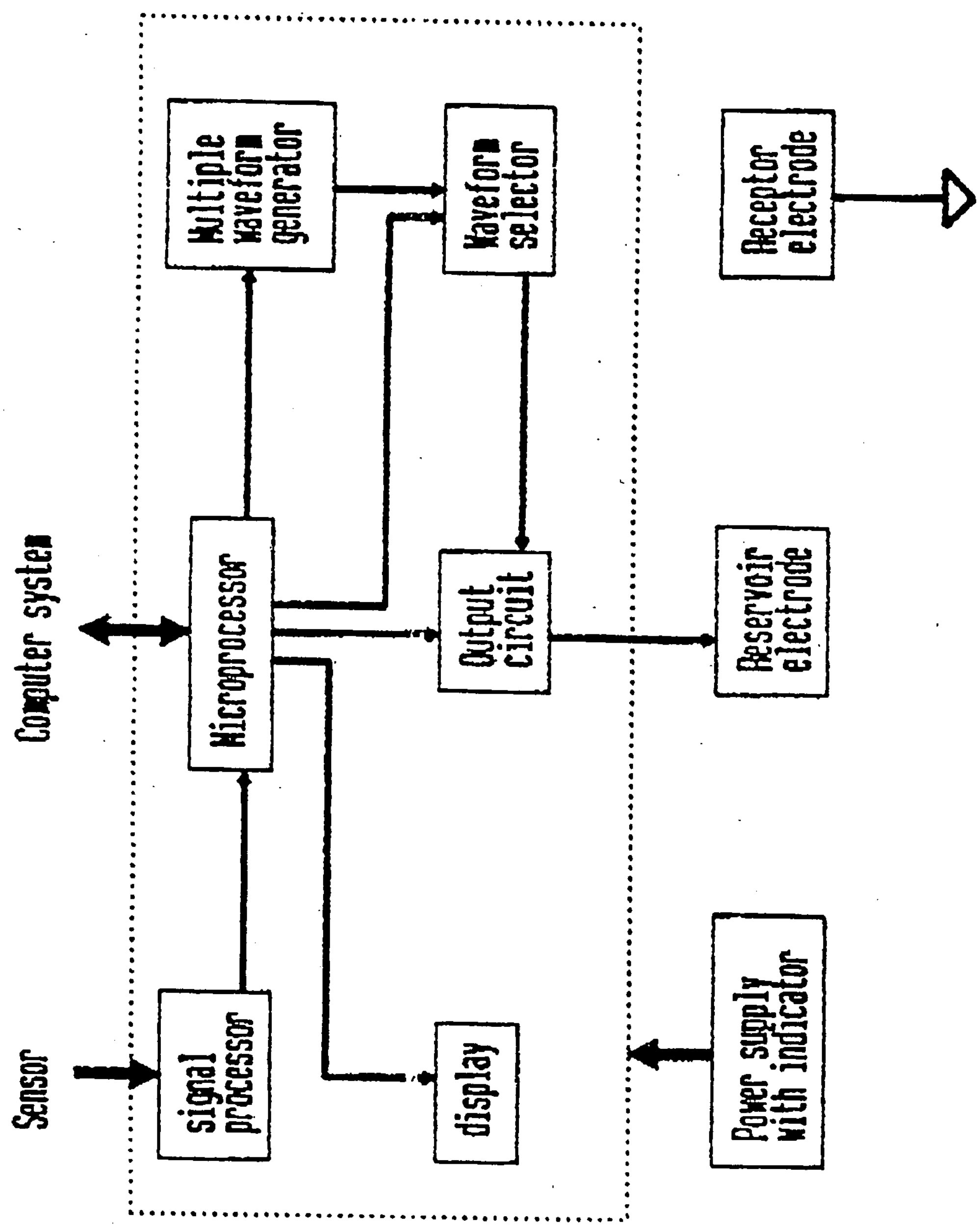

Computer system
Sensor
Microprocessor
signal processor
display
Multiple waveform generator
Waveform selector
Output circuit
Receptor electrode
Reservoir electrode
Power supply with indicator

Fig. 3

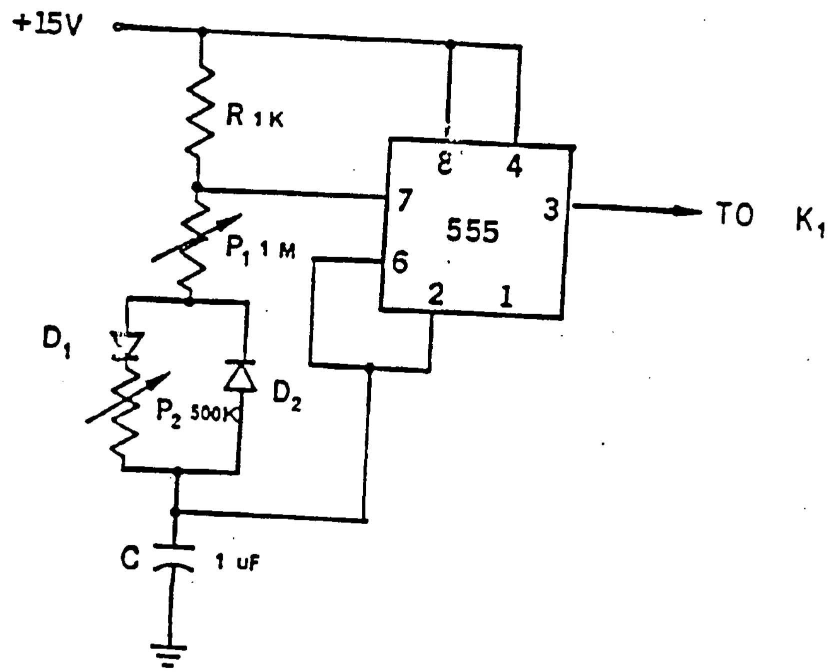


FIG. 4

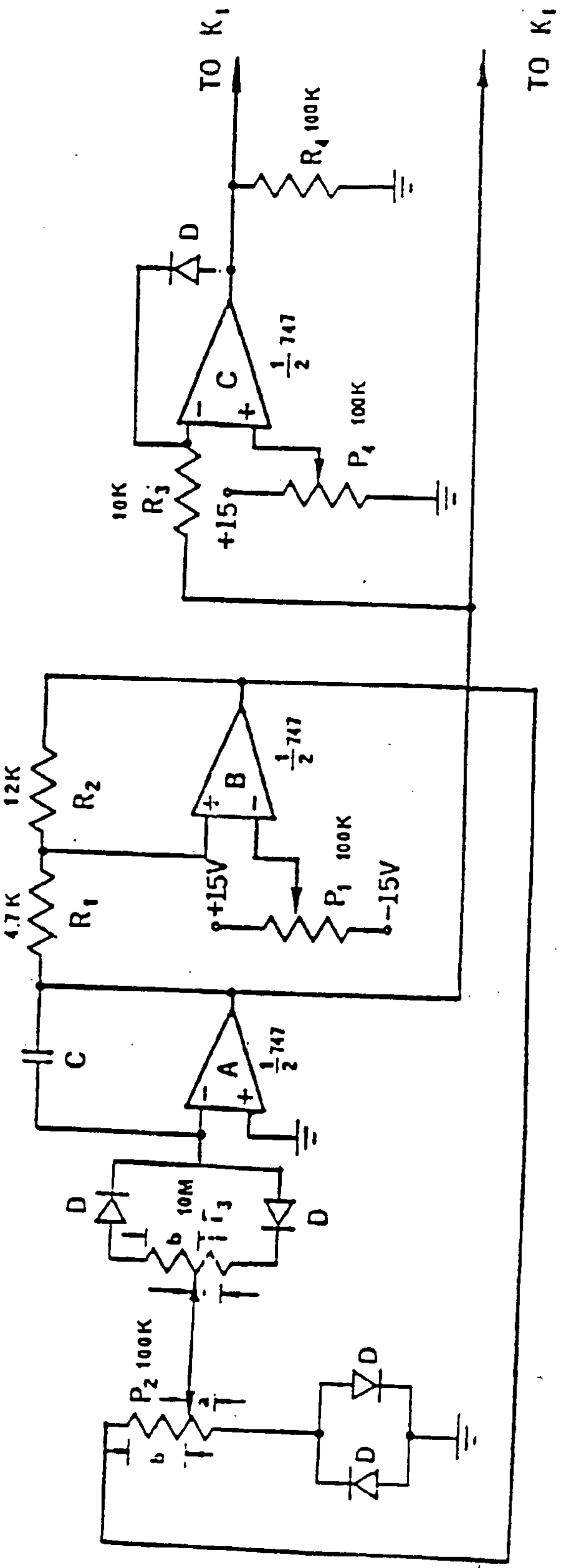

TO K1
TO K1
R4 100K
D
C
1/2 747
P4 100K
+15
R3
10K
12K
R2
4.7K
R1
B
1/2 747
+15V
P1 100K
-15V
C
A
1/2 747
D
10M
D
P2 100K
D
D

FIG. 5

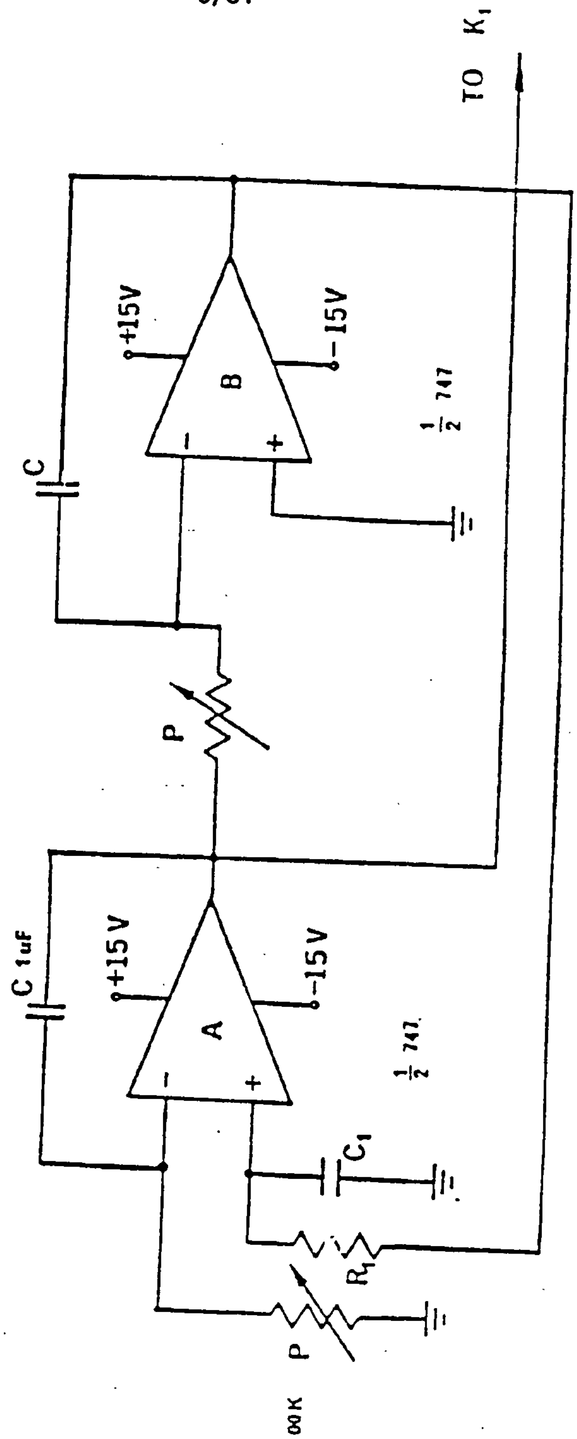


FIG. 6

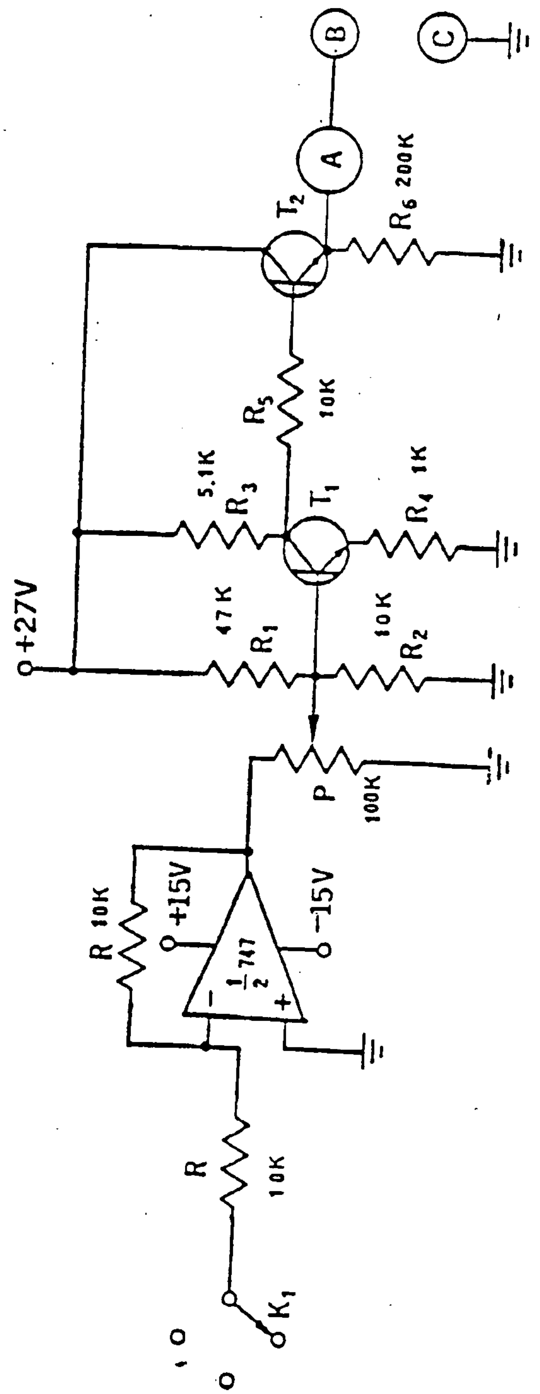

A
B
C
T_2
R_6 200K
R_5
10K
5.1K
R_3
T_1
R_4 1K
+27V
47K
R_1
10K
R_2
P
100K
R 10K
+15V
-15V
$\frac{1}{2}$ 747
R
10K
K_1

FIG. 7

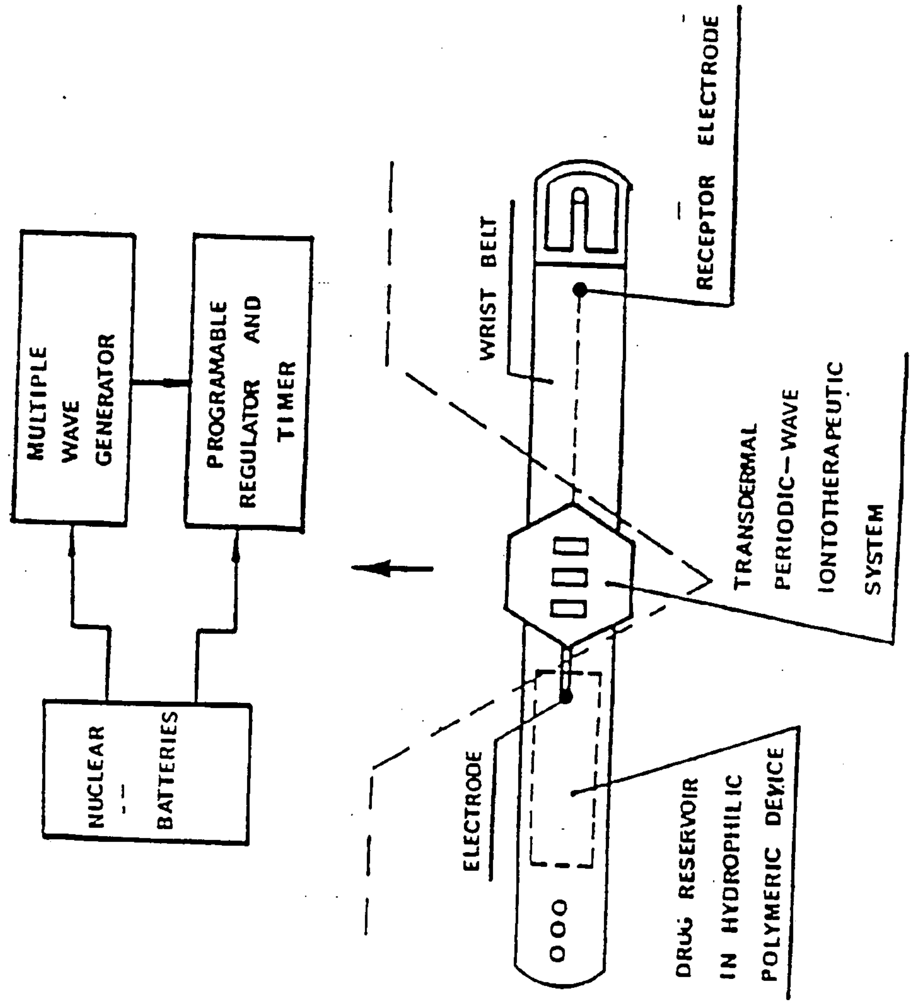

MULTIPLE WAVE GENERATOR
PROGRAMABLE REGULATOR AND TIMER
NUCLEAR -- BATTERIES
WRIST BELT
RECEPTOR ELECTRODE
TRANSDERMAL PERIODIC-WAVE IONTOTHERAPEUTIC SYSTEM
ELECTRODE
DRUG RESERVOIR IN HYDROPHILIC POLYMERIC DEVICE

FIG. 8

TRANSDERMAL PERIODIC IONTO-THERAPEUTIC SYSTEM

(TPIS)

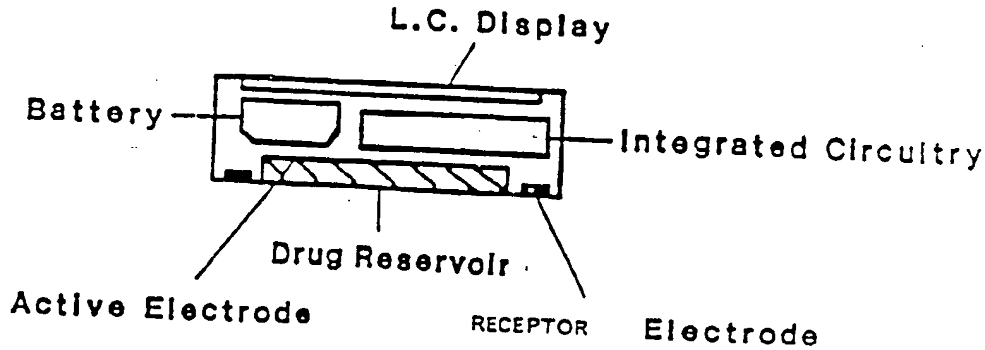


FIG. 9A

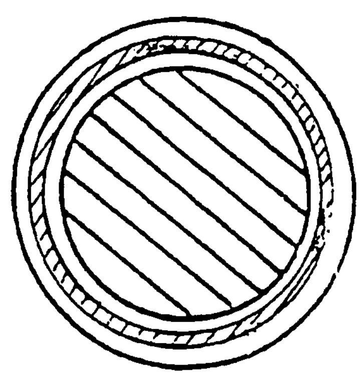


FIG. 9B

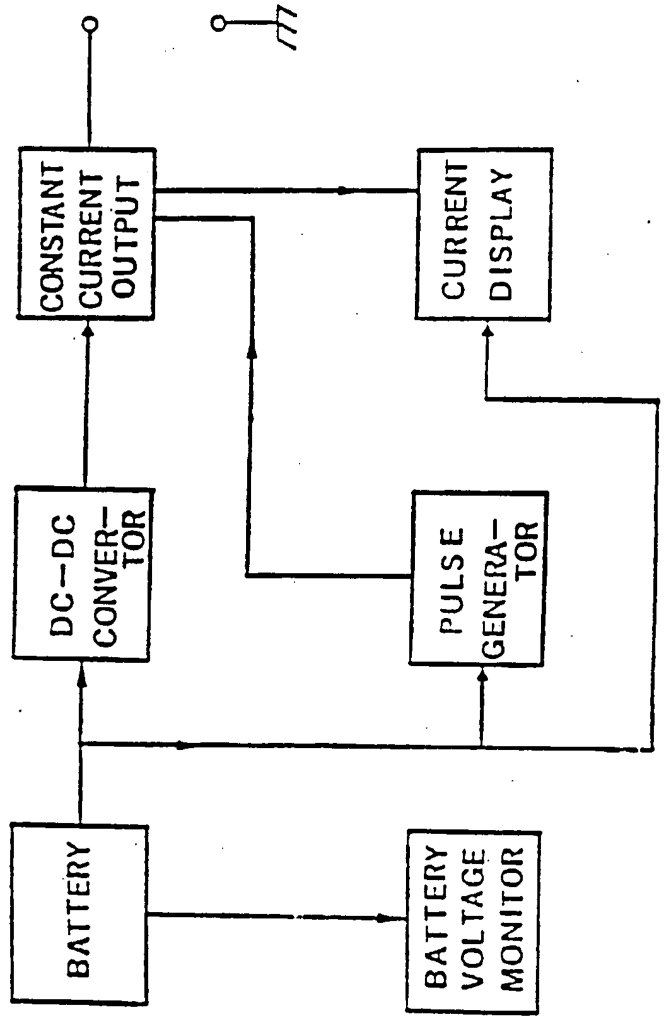

CONSTANT CURRENT OUTPUT
CURRENT DISPLAY
DC—DC CONVER-TOR
PULSE GENERA-TOR
BATTERY
BATTERY VOLTAGE MONITOR

FIG. 10

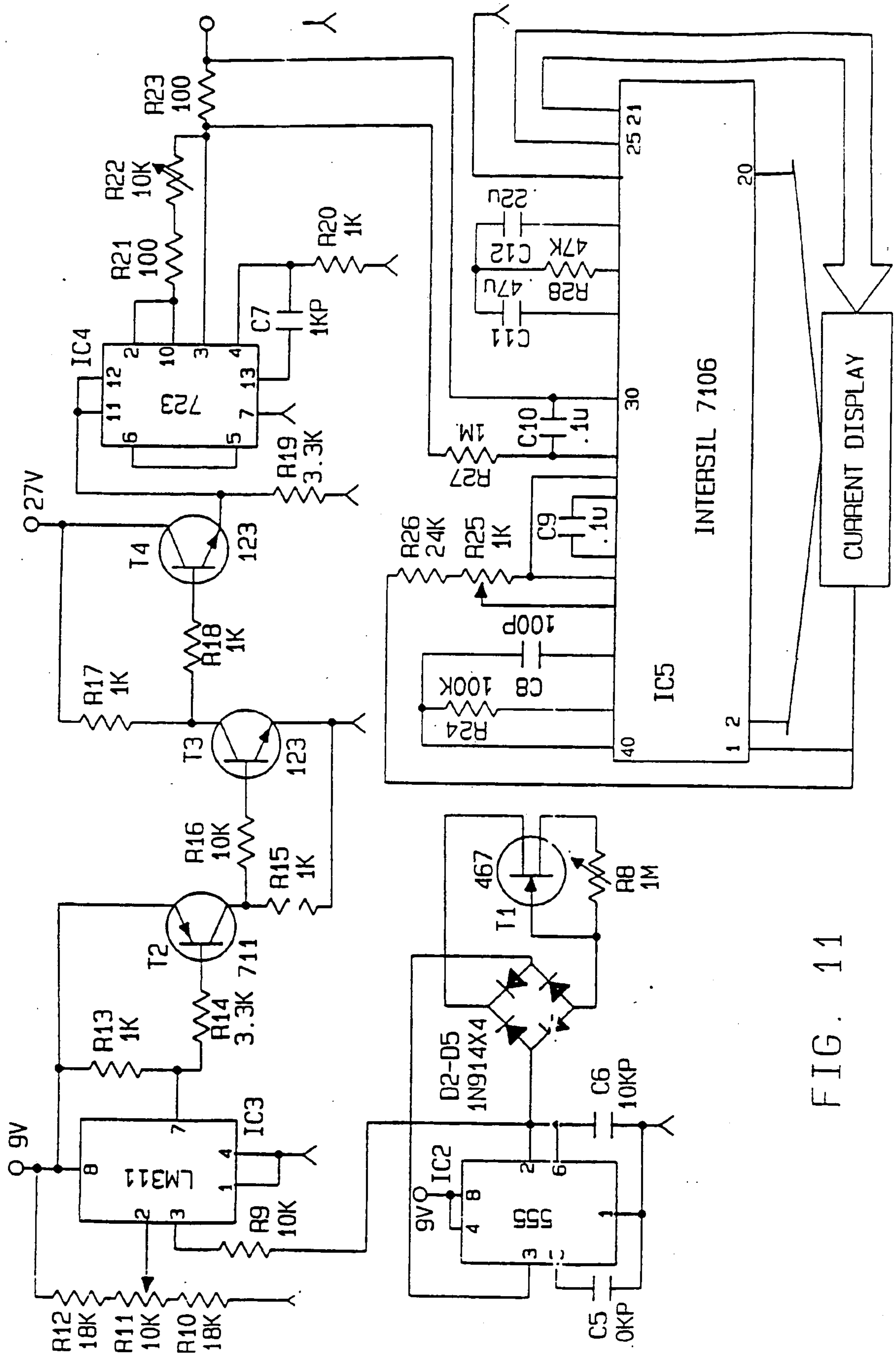

9V
27V
LM311
IC3
IC4
723
T2
711
T3
123
T4
123
T1
467
IC2
555
IC5
INTERSIL 7106
CURRENT DISPLAY
D2-D5
1N914X4
R8
1M
R9
10K
R10
18K
R11
10K
R12
18K
R13
1K
R14
3.3K
R15
1K
R16
10K
R17
1K
R18
1K
R19
3.3K
R20
1K
R21
100
R22
10K
R23
100
R24
100K
R25
1K
R26
24K
R27
1M
R28
47K
C5
0KP
C6
10KP
C7
1KP
C8
100P
C9
.1u
C10
.1u
C11
47u
C12
22u

FIG. 11

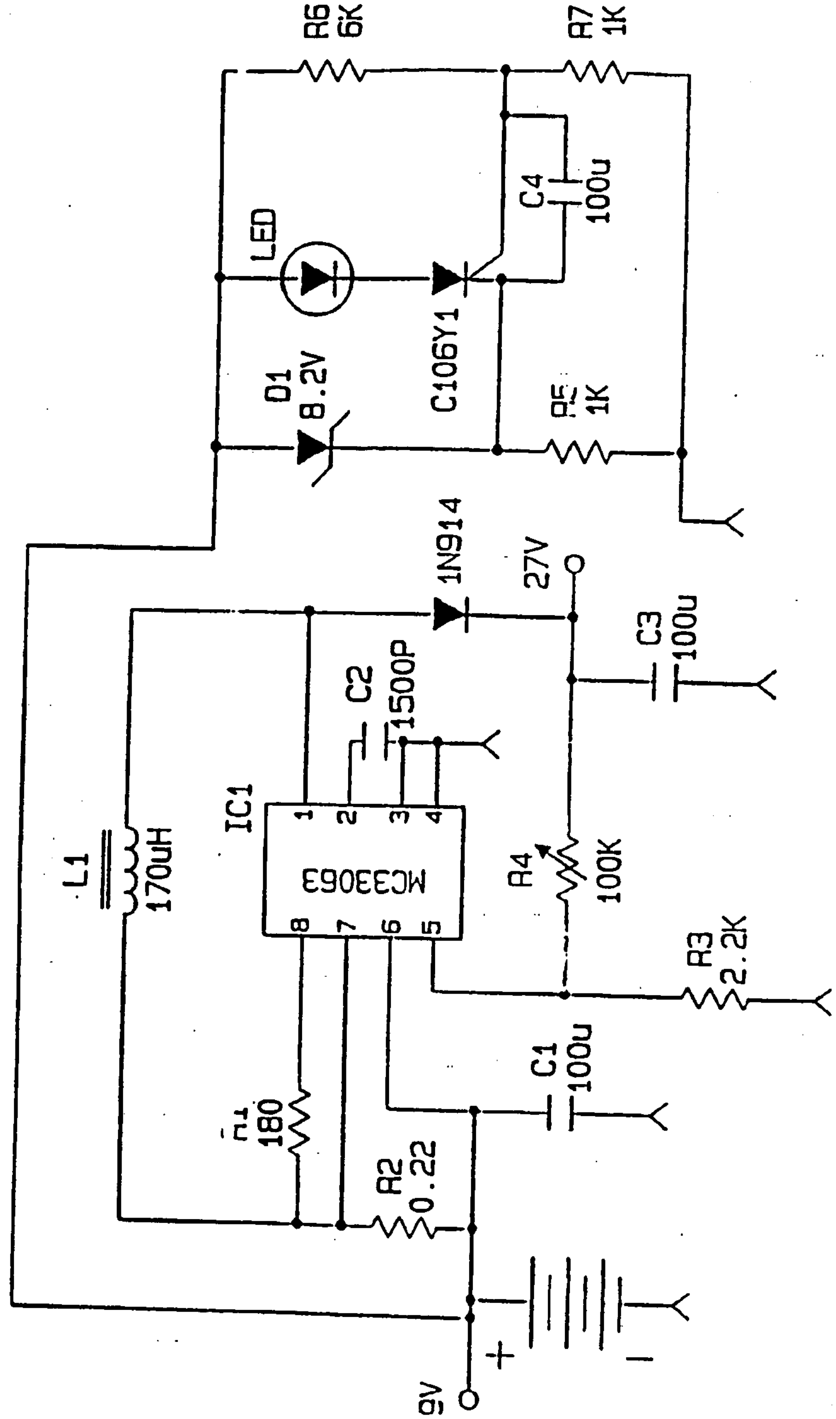

R6
6K
R7
1K
C4
100u
LED
C106Y1
D1
8.2V
R5
1K
1N914
27V
C3
100u
C2
1500P
IC1
MC33063
L1
170uH
R4
100K
R3
2.2K
C1
100u
R1
180
R2
0.22
9V
+
-

FIG. 11A

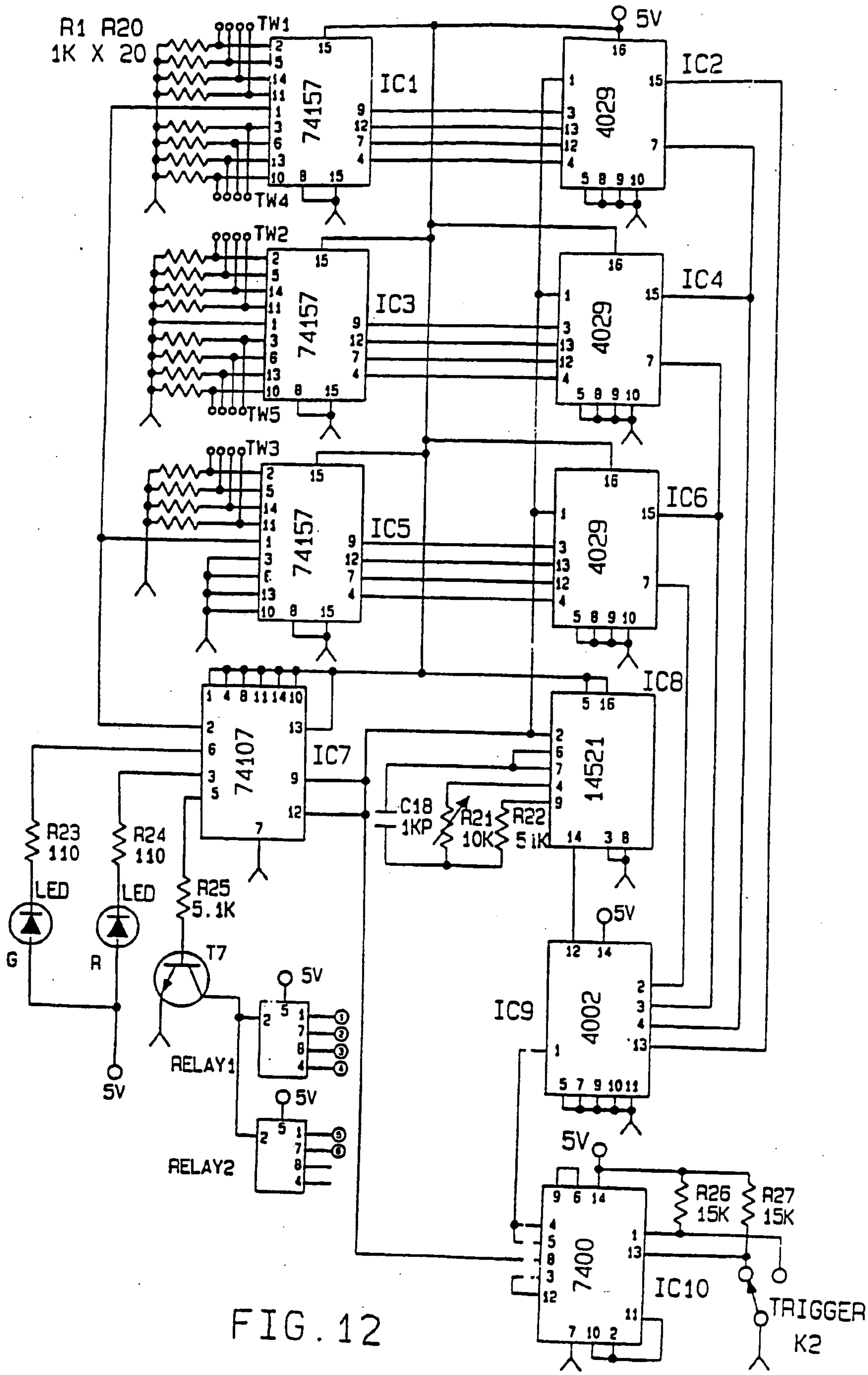

R1 R20
1K X 20
TW1
TW4
TW2
TW5
TW3
5V
IC1
74157
IC2
4029
IC3
74157
IC4
4029
IC5
74157
IC6
4029
IC7
74107
IC8
14521
C18
1KP
R21
10K
R22
5.1K
R23
110
R24
110
LED
LED
G
R
R25
5.1K
T7
5V
RELAY1
5V
RELAY2
IC9
4002
5V
R26
15K
R27
15K
7400
IC10
TRIGGER
K2

FIG. 12

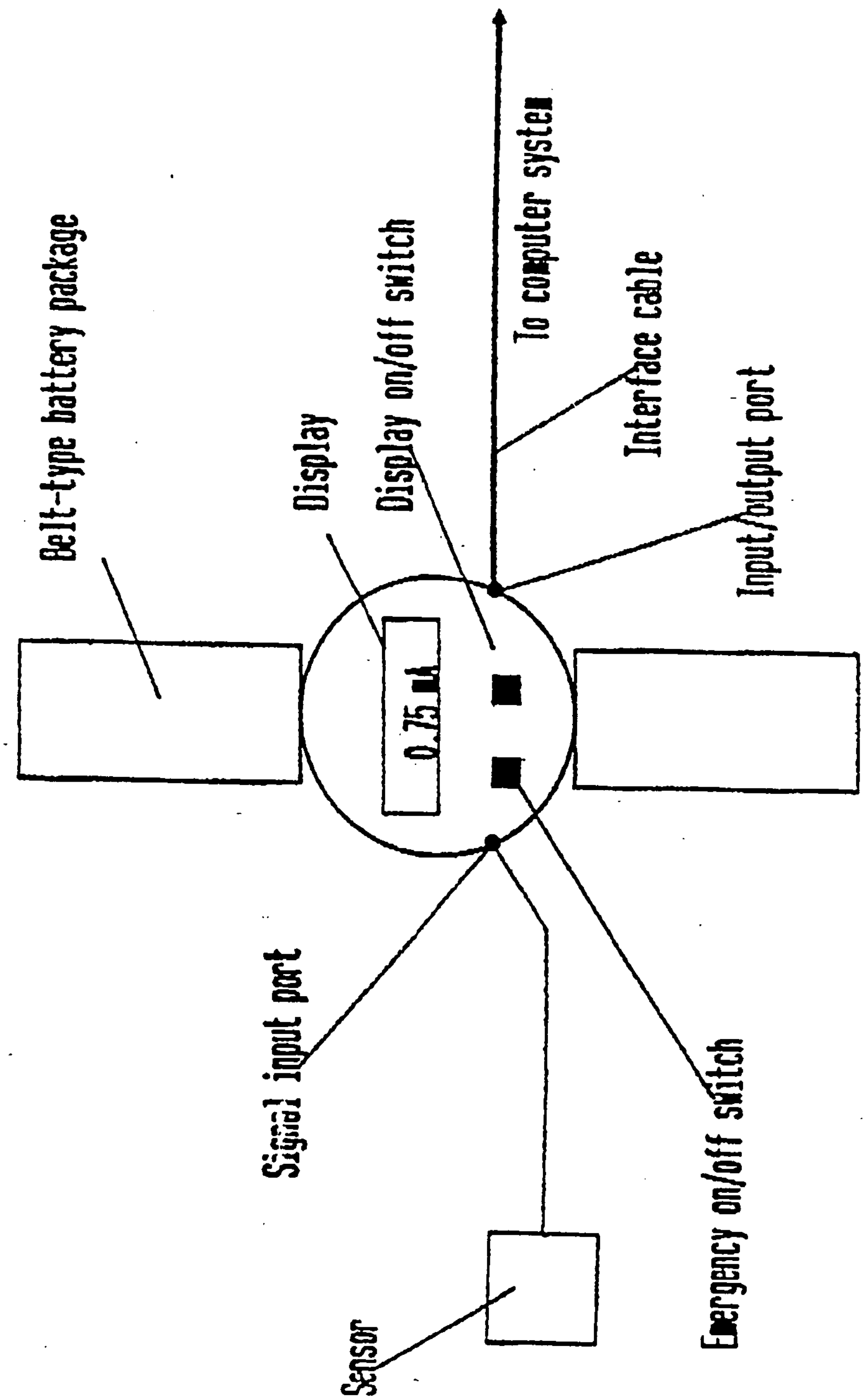

Belt-type battery package
Display
Display on/off switch
To computer system
Interface cable
Input/output port
0.75 mA
Signal input port
Emergency on/off switch
Sensor

Fig. 13

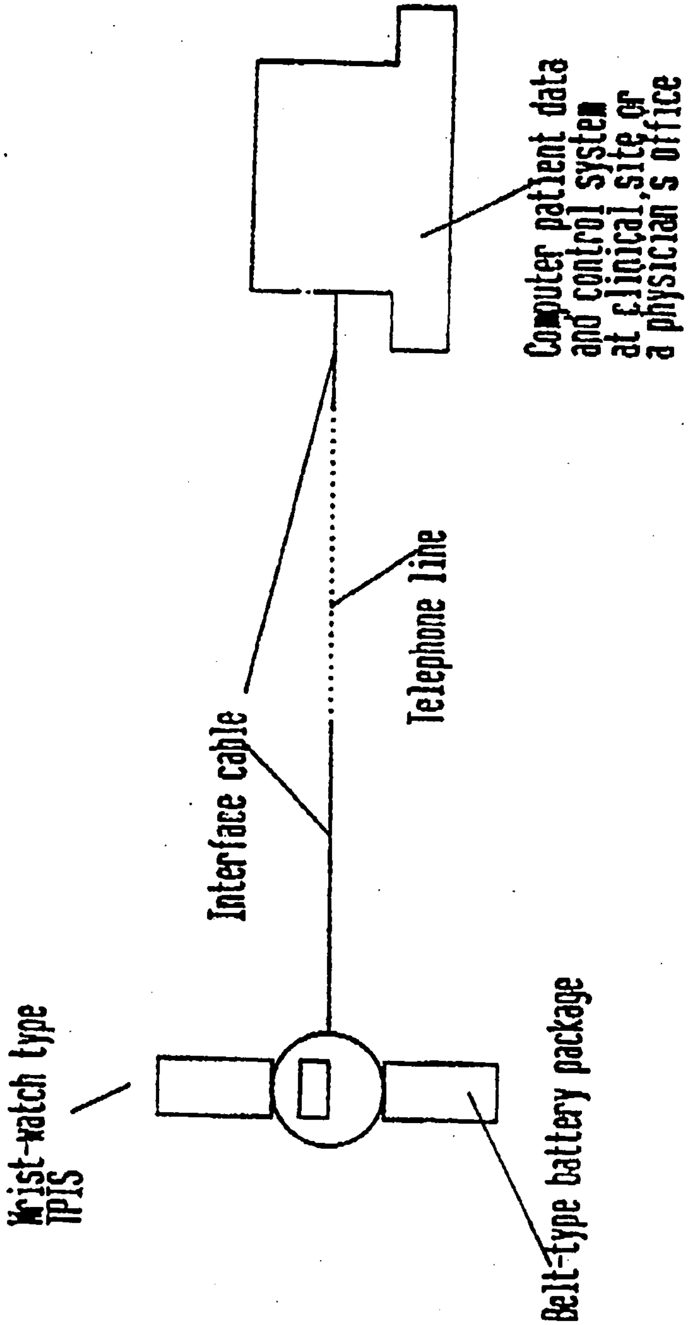

Computer patient data
and control system
at clinical site or
a physician's office
Telephone line
Interface cable
Wrist-watch type
TPIS
Belt-type battery package

Fig. 14

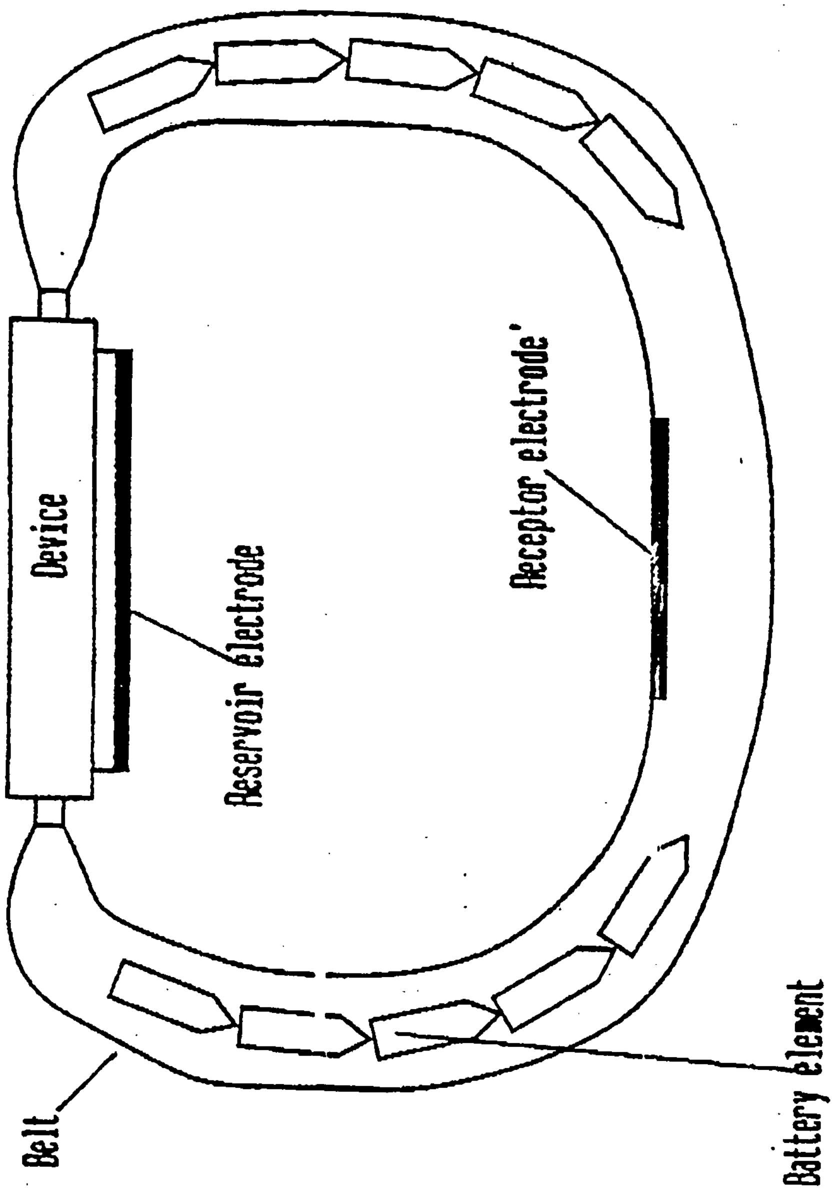

Device
Reservoir electrode
Receptor electrode'
Belt
Battery element

Fig. 15

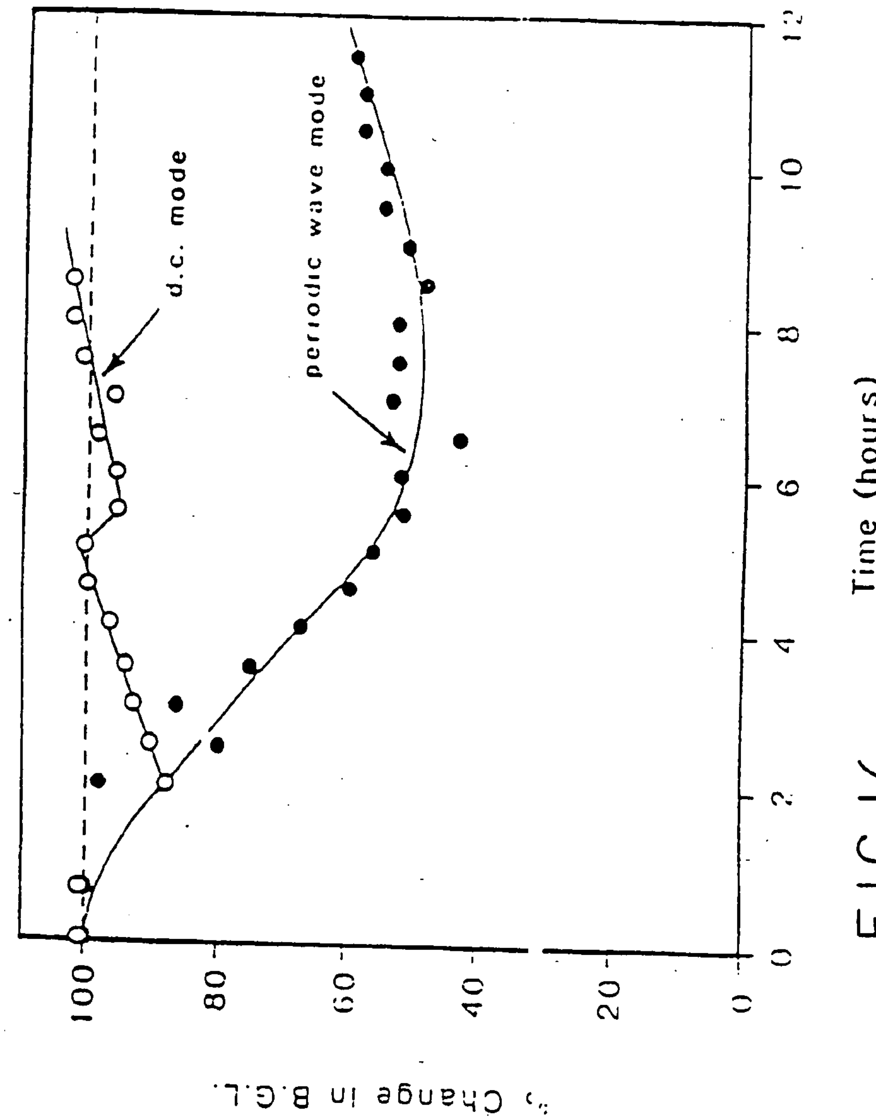
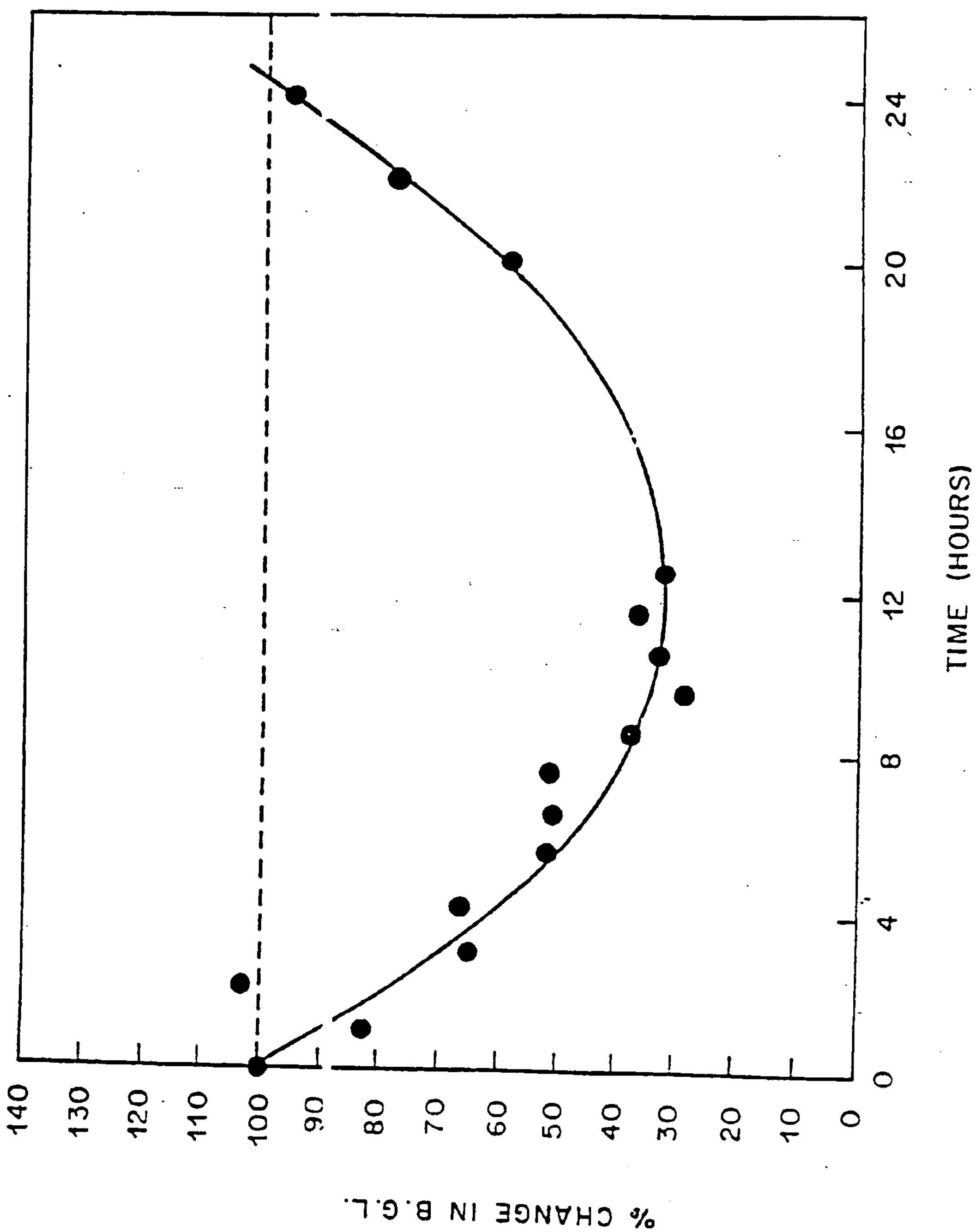

d.c. mode
periodic wave mode
Time (hours)
% Change in B.G.L.
0
20
40
60
80
100
0
2
4
6
8
10
12

FIG.16

FIG. 17


% CHANGE IN B.G.L.
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
TIME (HOURS)
0
4
8
12
16
20
24

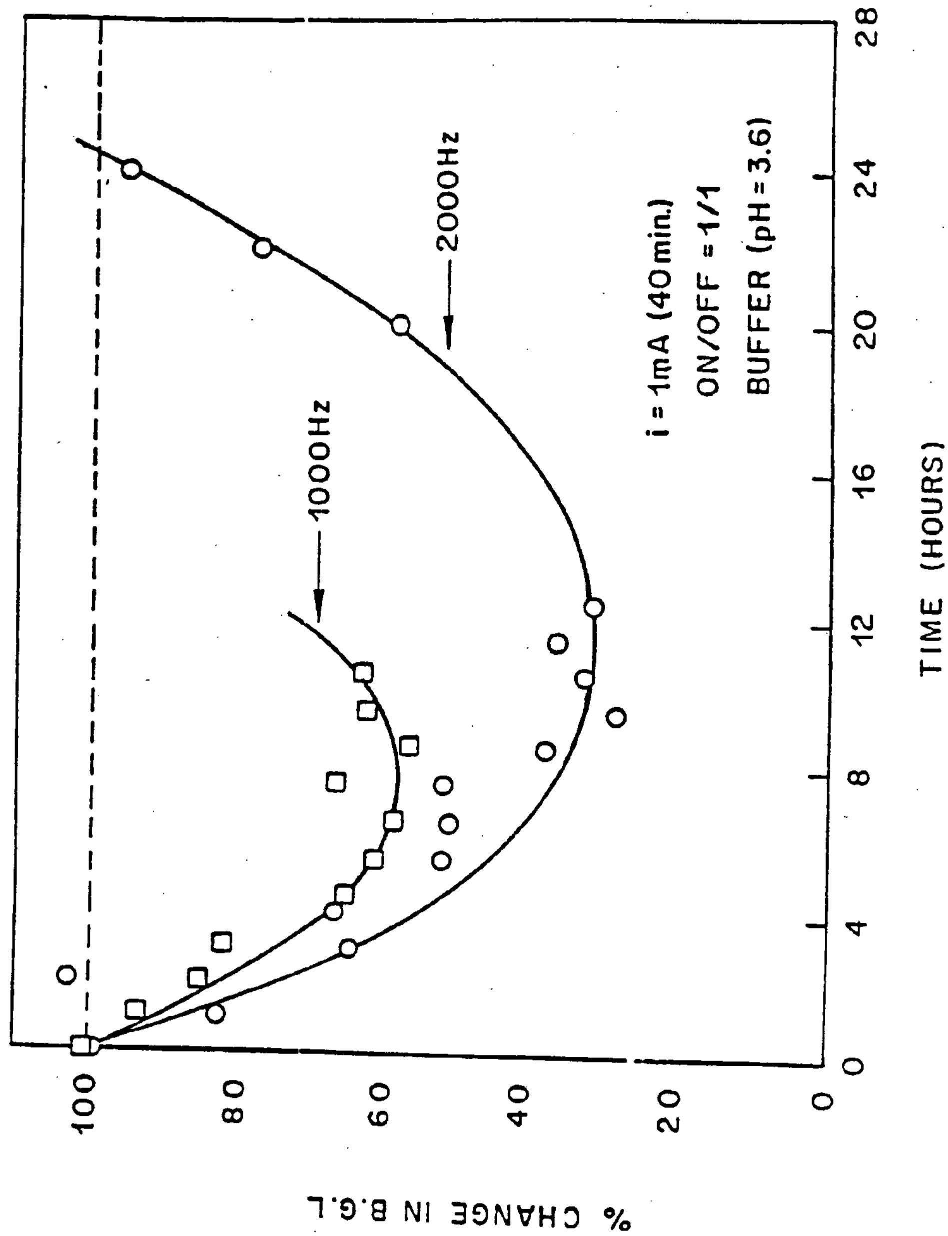
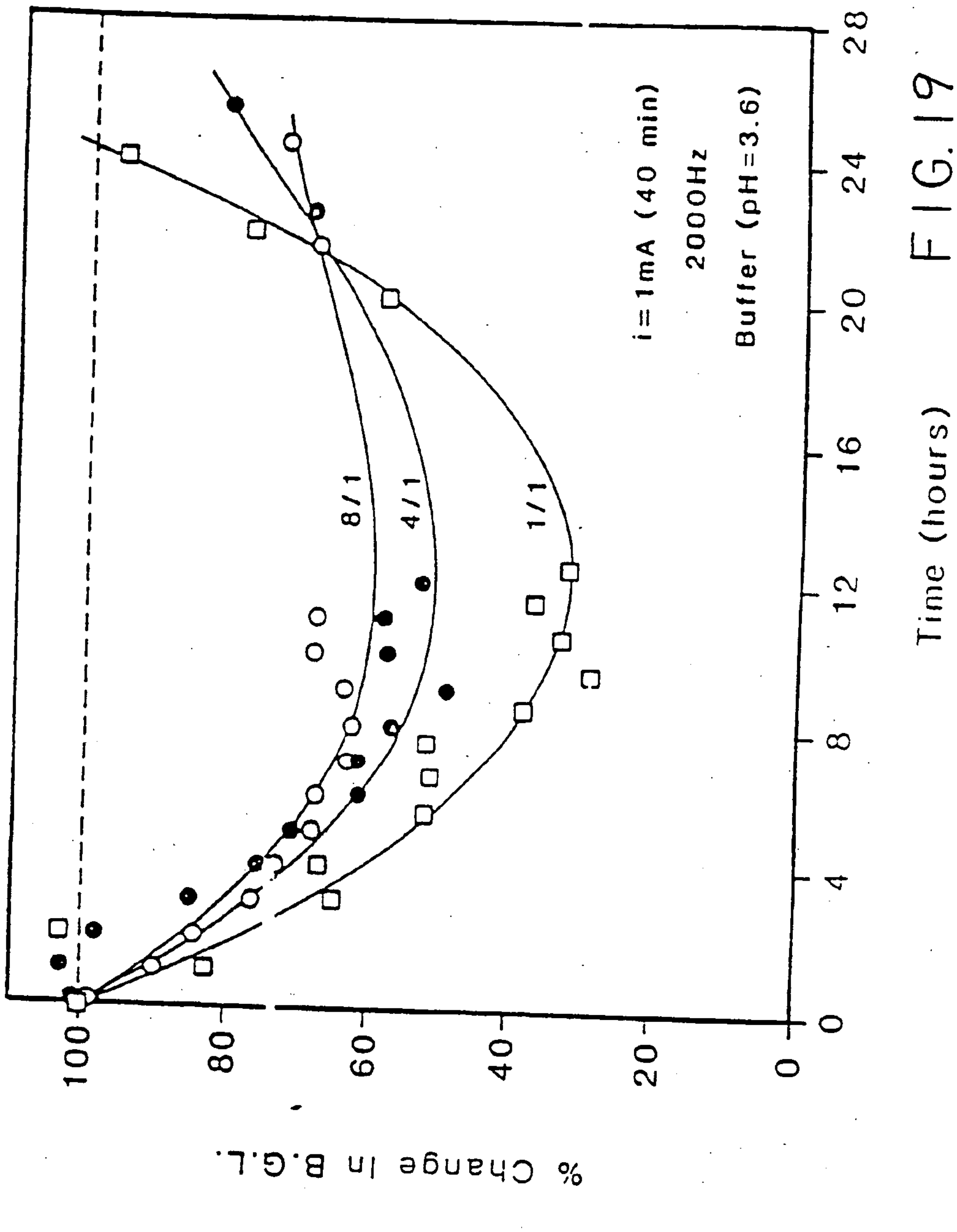

% CHANGE IN B.G.L
TIME (HOURS)
1000Hz
2000Hz
i = 1mA (40min.)
ON/OFF = 1/1
BUFFER (pH = 3.6)
0
20
40
60
80
100
0
4
8
12
16
20
24
28

FIG. 18



% Change in B.G.L.
100
80
60
40
20
0
0
4
8
12
16
20
24
28
Time (hours)
8/1
4/1
1/1
i=1mA (40 min)
2000Hz
Buffer (pH=3.6)

FIG. 19

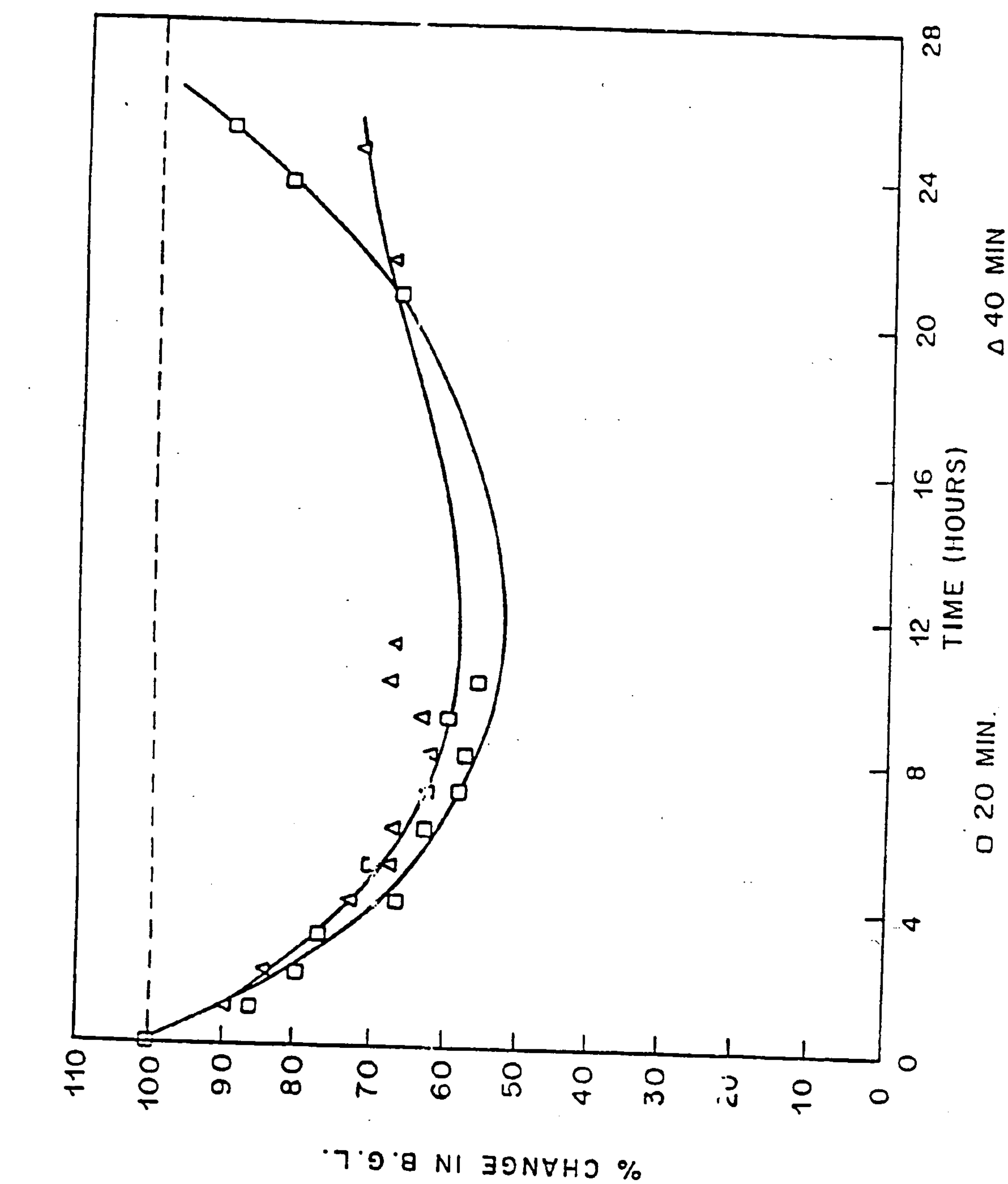

% CHANGE IN B.G.L.
110
100
90
80
70
60
50
40
30
20
10
0
0
4
8
12
16
20
24
28
TIME (HOURS)
□ 20 MIN.
Δ 40 MIN

FIG. 20

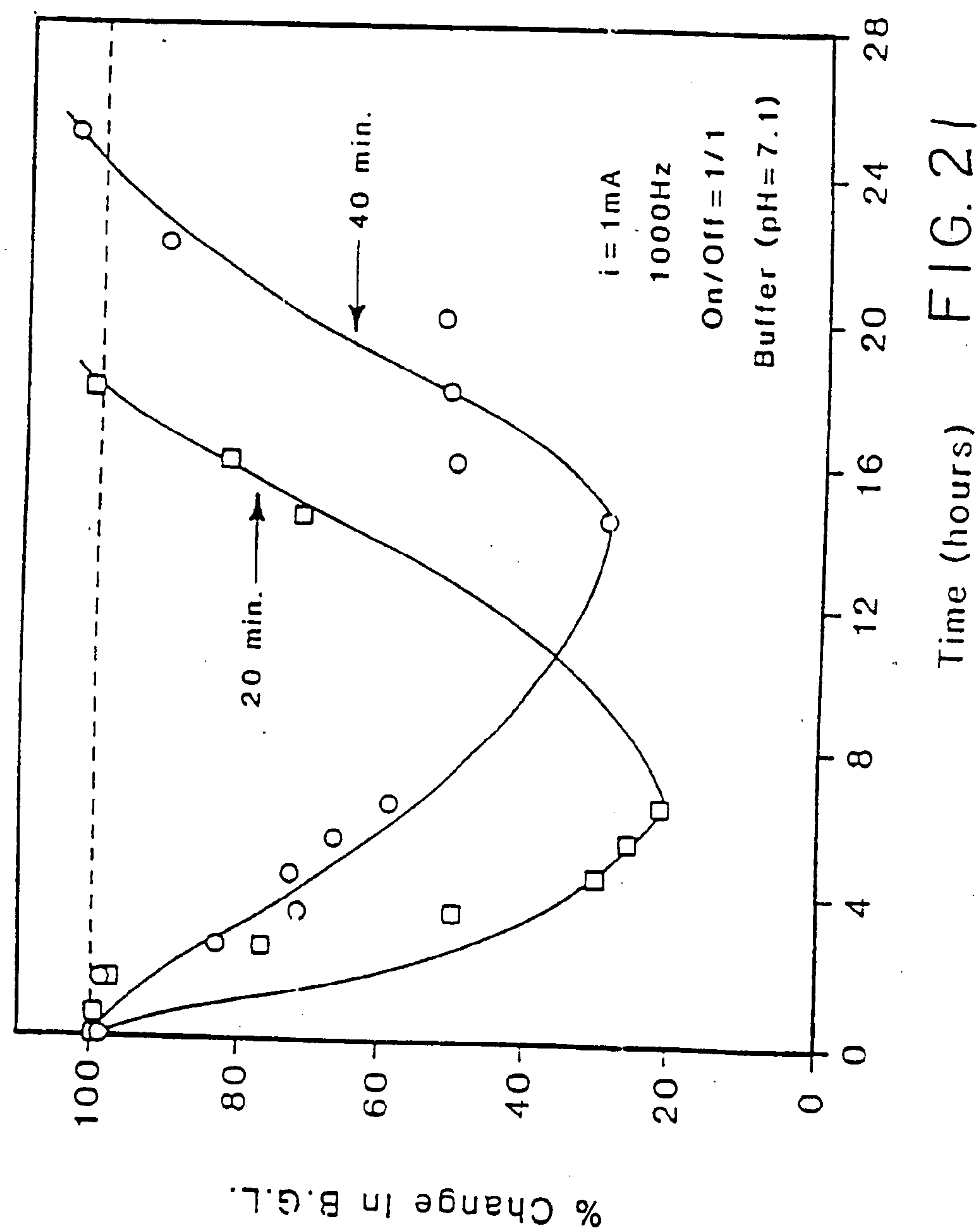

% Change in B.G.L.
100
80
60
40
20
0
Time (hours)
0
4
8
12
16
20
24
28
20 min.
40 min.
i = 1mA
1000Hz
On/Off = 1/1
Buffer (pH = 7.1)

FIG. 21

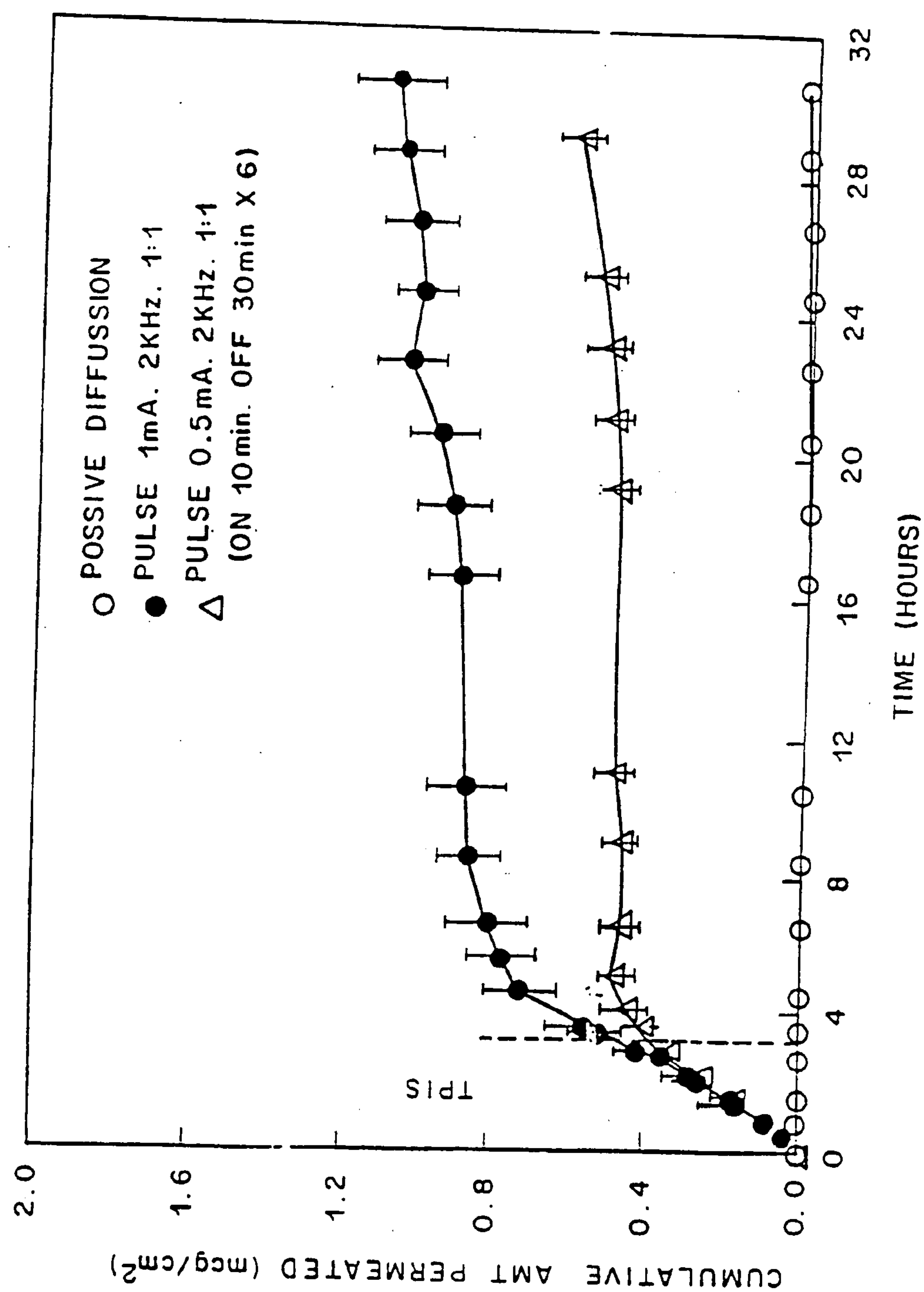

POSSIVE DIFFUSSION
PULSE 1mA. 2KHz. 1:1
PULSE 0.5mA. 2KHz. 1:1
(ON 10min. OFF 30min X 6)
TPIS
CUMULATIVE AMT PERMEATED (mcg/cm2)
2.0
1.6
1.2
0.8
0.4
0.0
0
4
8
12
16
20
24
28
32
TIME (HOURS)

FIG. 22

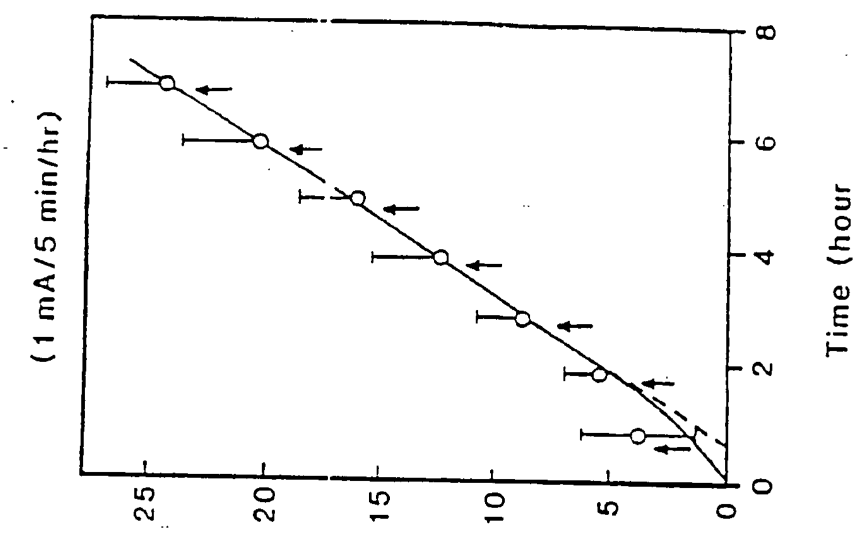


FIG.23B

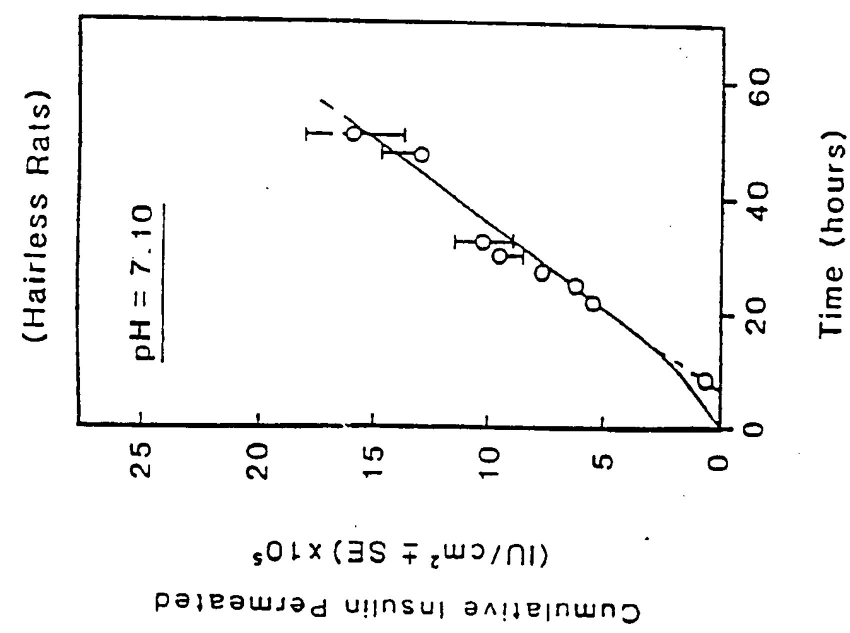
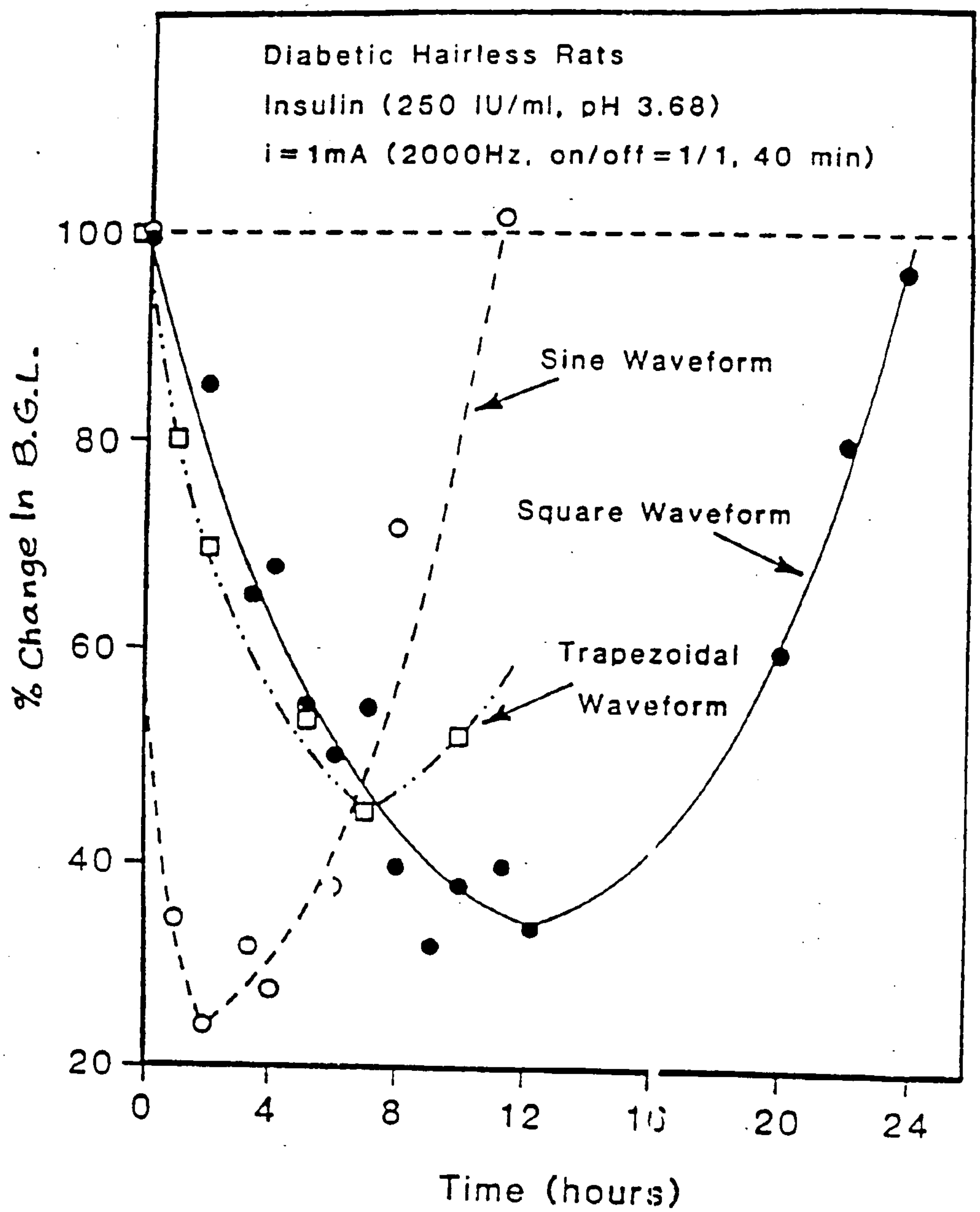


FIG.23A


Diabetic Hairless Rats
Insulin (250 IU/ml, pH 3.68)
i=1mA (2000Hz, on/off=1/1, 40 min)
% Change In B.G.L.
100
80
60
40
20
Sine Waveform
Square Waveform
Trapezoidal Waveform
0
4
8
12
20
24
Time (hours)

F I G. 24

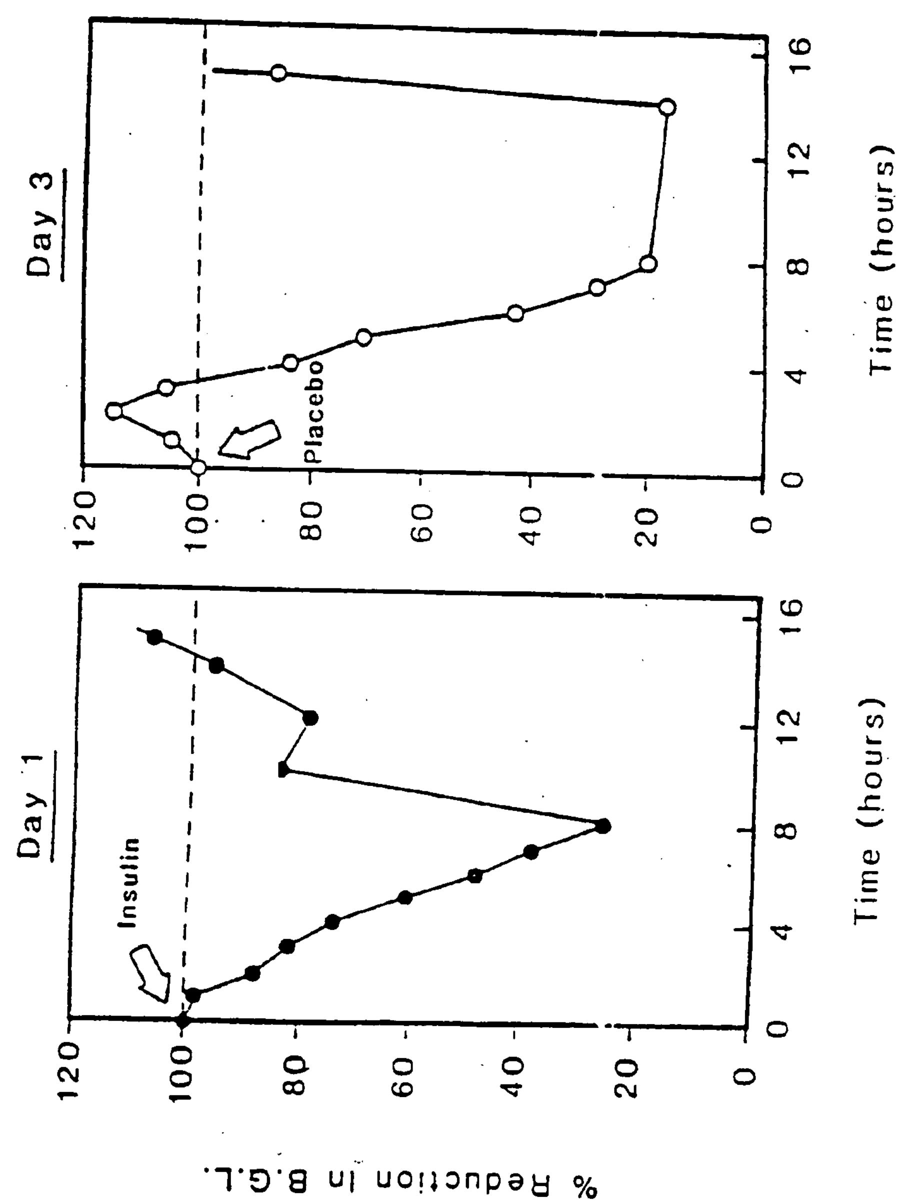


FIG.25A

FIG.25B

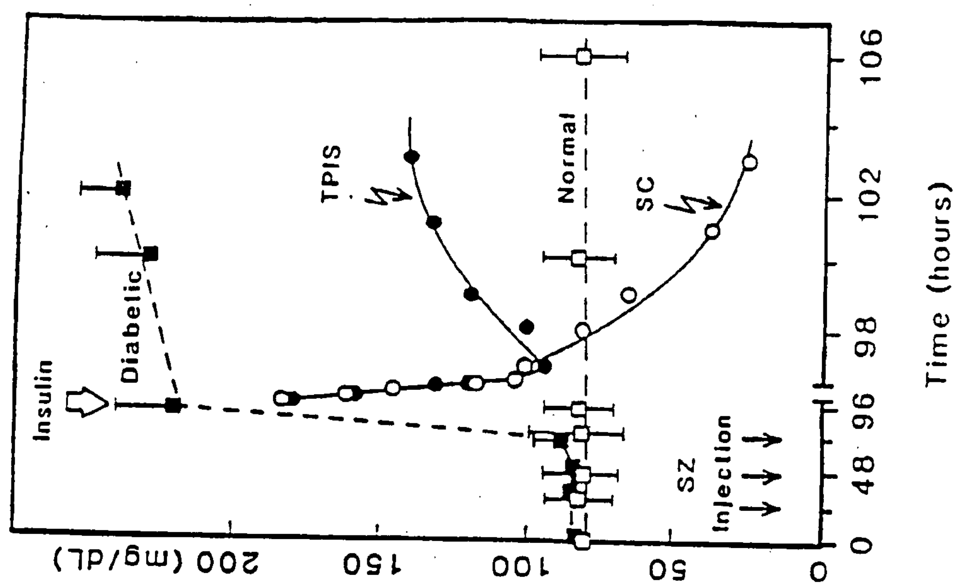


FIG. 26B

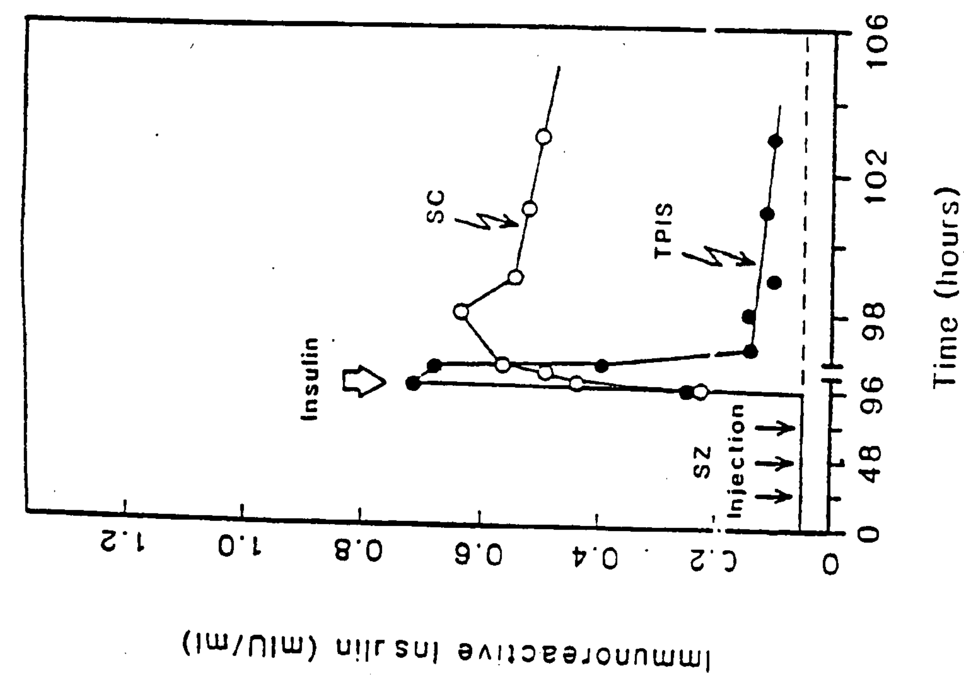


FIG. 26A

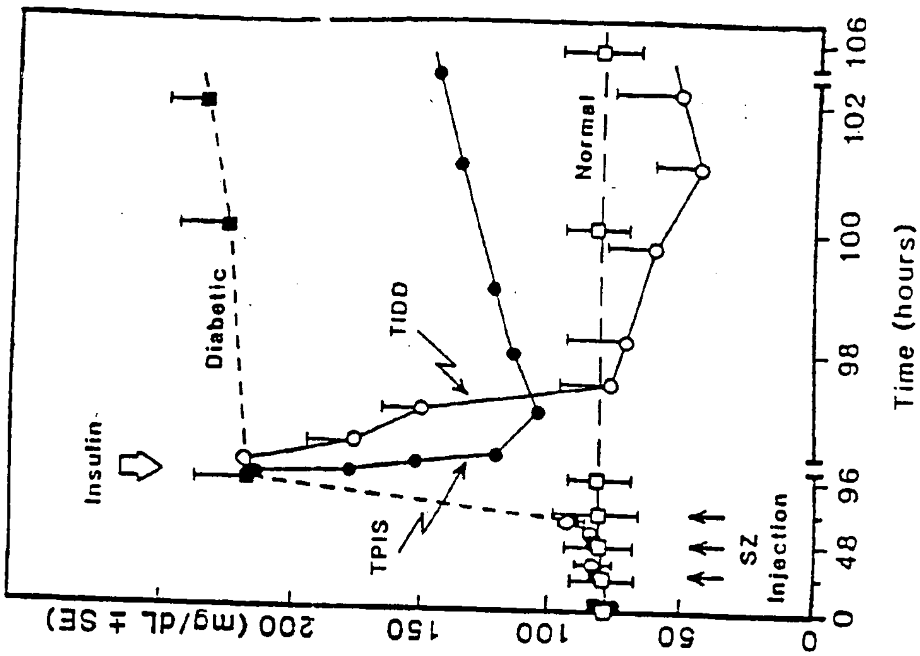


FIG.27B

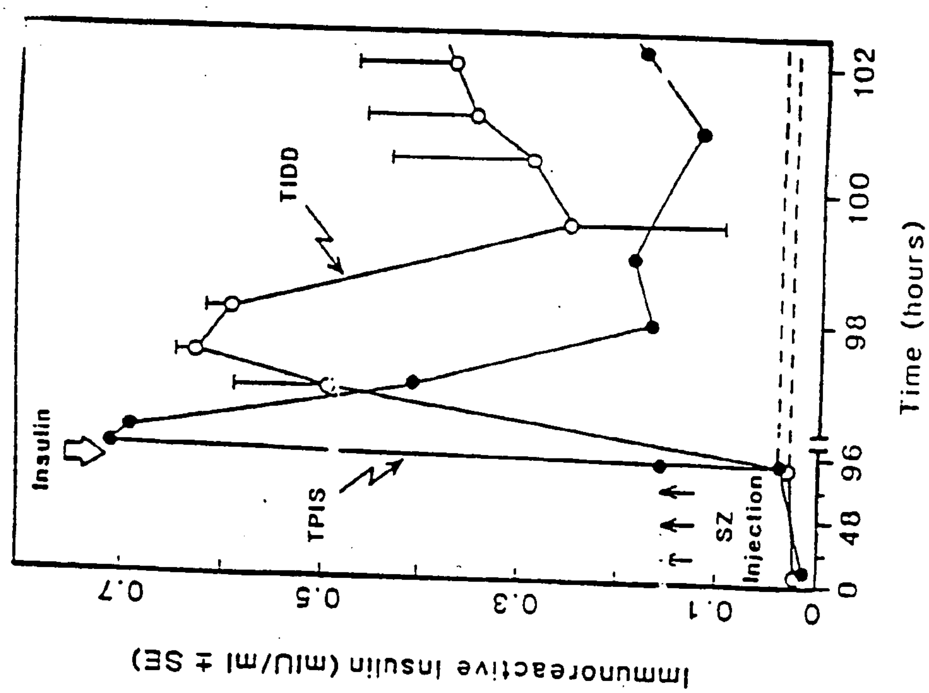


FIG.27A

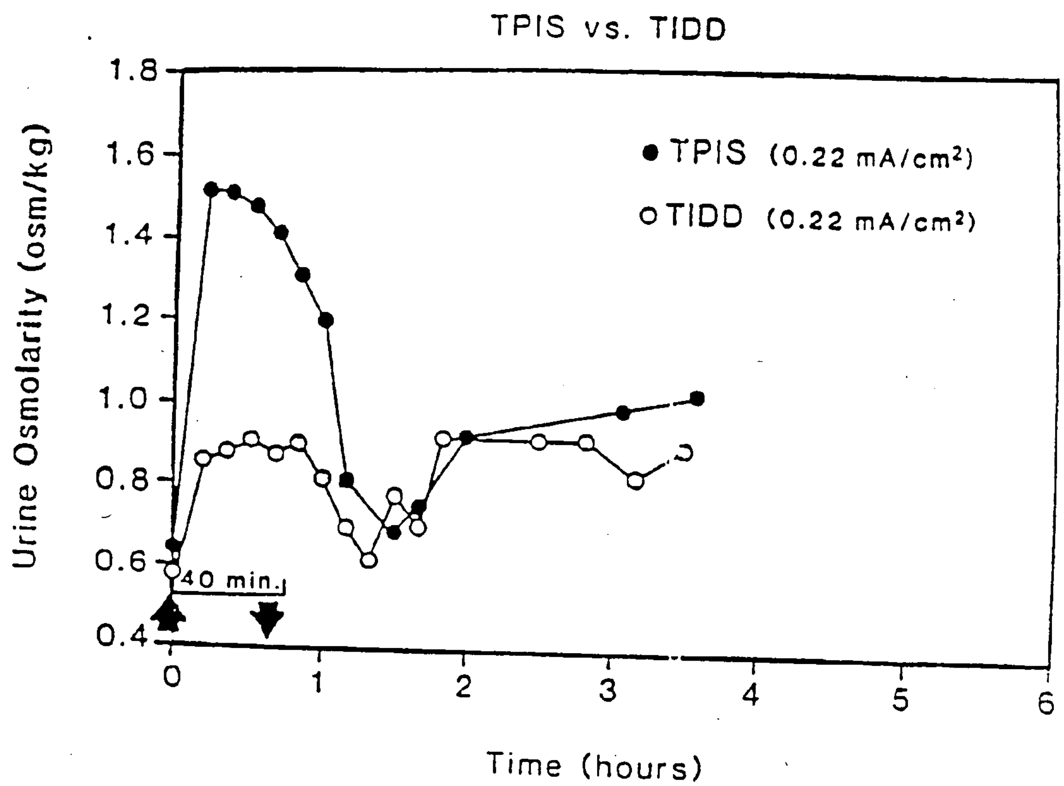

TPIS vs. TIDD
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
Urine Osmolarity (osm/kg)
● TPIS (0.22 mA/cm²)
○ TIDD (0.22 mA/cm²)
40 min.
0
1
2
3
4
5
6
Time (hours)

FIG. 28

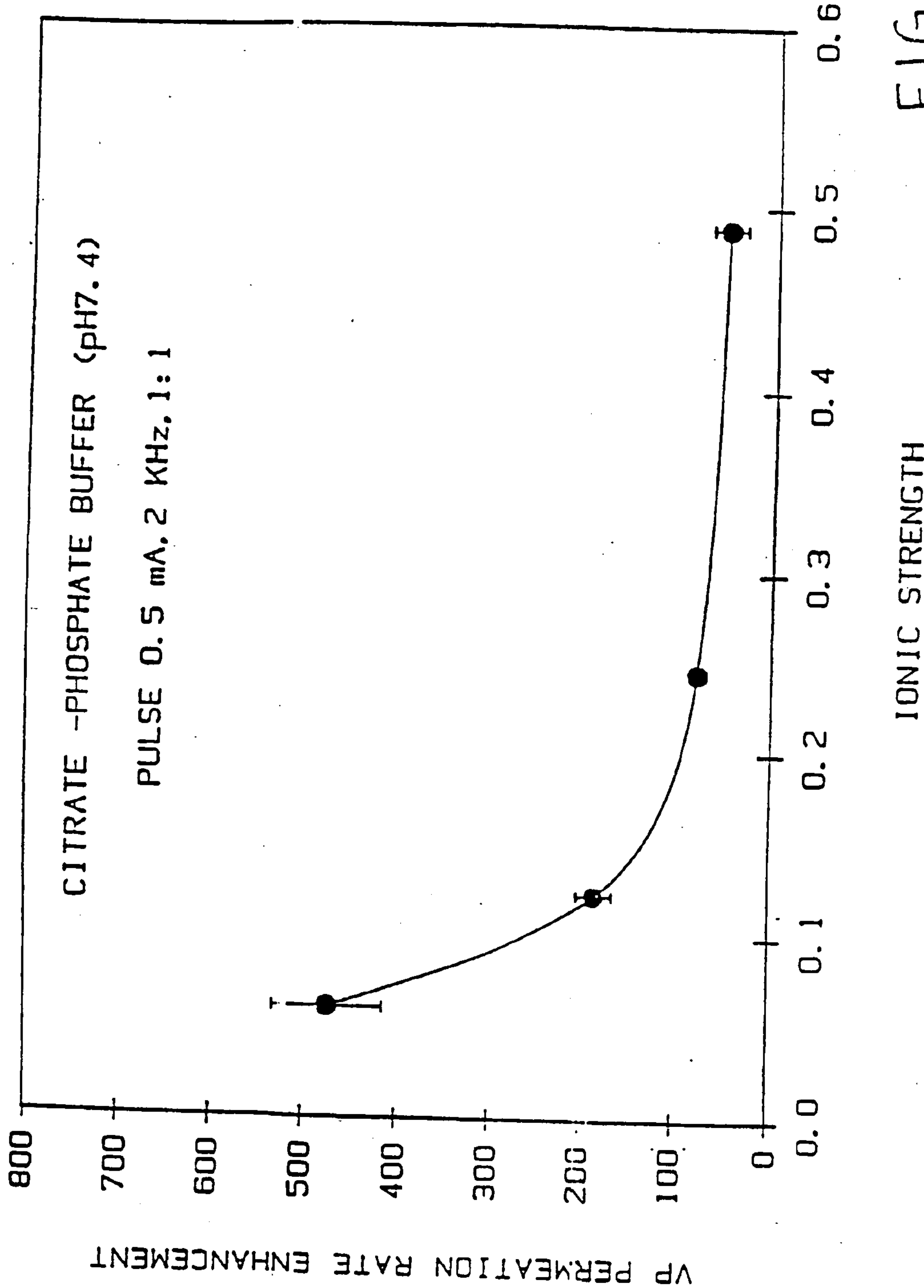

CITRATE -PHOSPHATE BUFFER (pH7.4)
PULSE 0.5 mA, 2 KHz, 1:1
VP PERMEATION RATE ENHANCEMENT
800
700
600
500
400
300
200
100
0
0.0
0.1
0.2
0.3
0.4
0.5
0.6
IONIC STRENGTH

FIG. 29

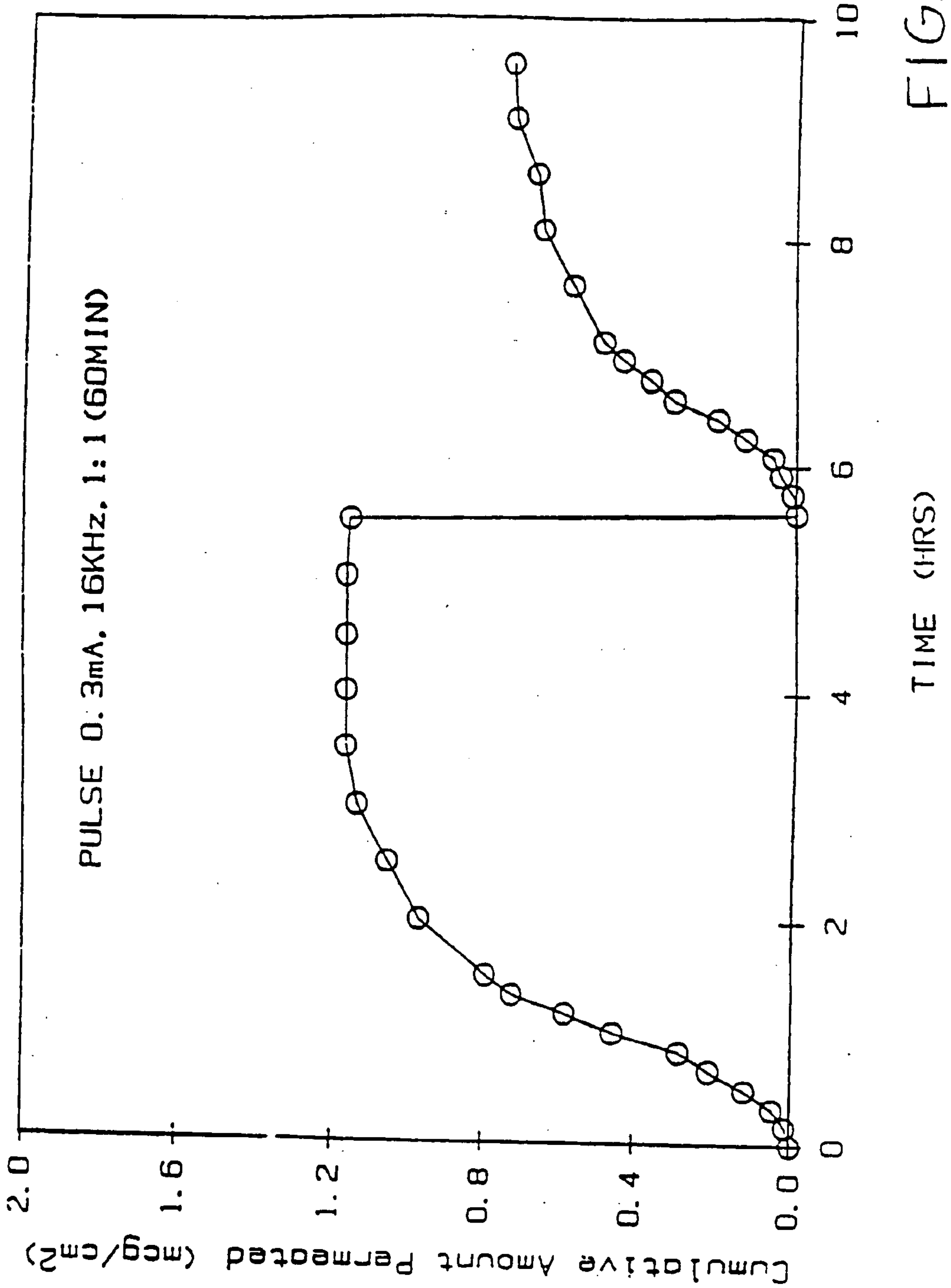

PULSE 0.3mA, 16KHz, 1:1 (60MIN)
Cumulative Amount Permeated (mcg/cm2)
2.0
1.6
1.2
0.8
0.4
0.0
0
2
4
6
8
10
TIME (HRS)

FIG.30

INTERNATIONAL SEARCH REPORT

PCT/US92/07221

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61N 1/30
US CL :604/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/748,802,803

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	US,A, 5,042,975 (CHEIN ET AL) 27 AUGUST 1991 See entire document	1-19
Y	US,A, 4,722,726 (SANDERSON ET AL) 02 FEBRUARY 1988 See column 7, lines 10-16	1-17
Y	WO,A, 86/07268 (SIBALIS) 18 DECEMBER 1986 See entire document	1-17
A	WO,A, 86/07269 (MCNICHOLS ET AL) 16 FEBRUARY 1988 See Abstract	1-17

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 NOVEMBER 1992	31 DEC 1992

Name and mailing address of the ISA/	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Andre Kalinan MICHAEL RAFA
Facsimile No. NOT APPLICABLE	Telephone No. (703) 308-2214

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A, 4,931,046 (NEWMAN) 05 JUNE 1990 See Abstract	1-17
A	US,A, 5,013,293 (SIBALIS) 07 MAY 1991 See entire document	1-17
A	US,A, 5,135,479 (SIBALIS ET AL) 04 AUGUST 1992 See entire document	1-19
A	WO, A, 86/07269 (SIBALIS ET AL.) 18 DECEMBER 1986. See entire document	1-17
A	US,A, 4,942,883 (NEWMAN) 24 JULY 1990. See Abstract, Figures)	1-17